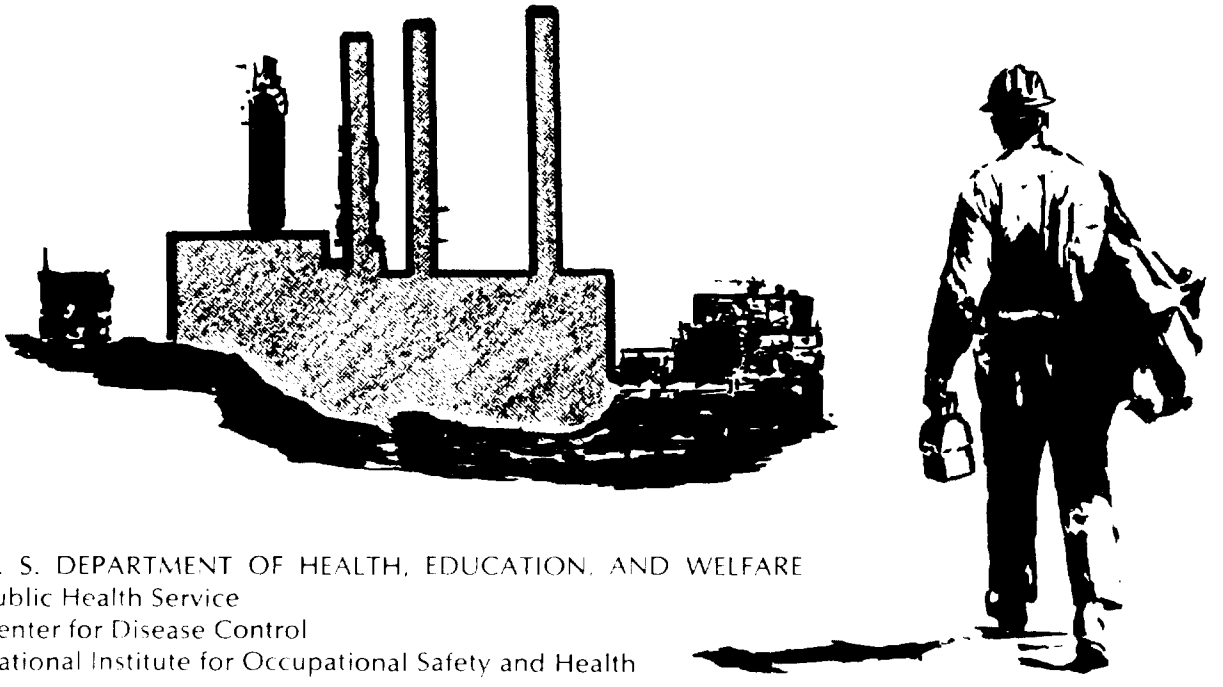
NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE TO

KETONES



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO KETONES

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

June 1978

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

DISCLAIMER

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

DHEW (NIOSH) Publication No. 78-173

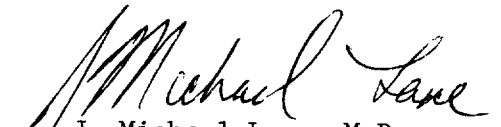
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on ketones by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the American Academy of Industrial Hygiene, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.



J. Michael Lane, M.D.
Acting Director, National Institute
for Occupational Safety and Health

The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for ketones. Burt J. Cooper of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31.

The Division review of this document was provided by Keith H. Jacobson, Ph.D. (Chairman), Jon R. May, Ph.D., Barry L. Johnson, Ph.D. (Division of Biomedical and Behavioral Science), P.G. Rentos, Ph.D. (Division of Training and Manpower Development), Harold Resnick, Ph.D. (Division of Respiratory Disease Studies), Theodore Thoburn, M.D. (Division of Surveillance, Hazard Evaluations, and Field Studies), and Clara H. Williams, Ph.D.

REVIEW CONSULTANTS

Norman Allen, M.D.
Professor of Neurology
Director, Division of Neurology
Ohio State University College of Medicine
Columbus, Ohio 43210

Roy L. Barnes
Secretary-Treasurer, Local 4-367
Oil, Chemical, and Atomic Workers
International Union
Pasadena, Texas 77502

Donald J. Billmaier, M.D.
Assistant Medical Director
Owens Corning Fiberglas Corporation
Toledo, Ohio 43659

Robert S. Brookman, Ph.D.
Manager, Research, Development, and
Technical Service
Firestone Plastics Company
Pottstown, Pennsylvania 19464

Daniel Couri, Ph.D.
Professor of Pharmacology
Ohio State University College of Medicine
Columbus, Ohio 43210

George D. DiVincenzo, Ph.D.
Technical Associate, Health, Safety, and
Human Factors Laboratory
Eastman Kodak Company
Rochester, New York 14650

James D. MacEwen, Ph.D.
Director, Toxic Hazards Research Unit
University of California, Irvine
Dayton, Ohio 45431

Leonard D. Pagnotto
Chief of Chemical Services
Massachusetts Dept of Labor and Industries
Division of Occupational Hygiene
Boston, Massachusetts 02116

FEDERAL AGENCIES

Department of Defense
  Office of Assistant Secretary of Defense
    Energy and Environmental Safety

  Department of the Army
    Army Environmental Hygiene Agency

  Department of the Navy
    Bureau of Medicine and Surgery
      Navy Environmental Health Center

  Department of the Air Force
    Office of the Surgeon General
    Occupational and Environmental Health Laboratories
    Inspection and Safety Center

Department of Energy
  Division of Operational and Environmental Safety

Department of Health, Education, and Welfare
  National Institutes of Health
    National Institute of Neurological and
      Communicative Disorders and Stroke

Department of Treasury
  Bureau of Engraving and Printing

Environmental Protection Agency
  Office of Assistant Administrator for
    Research and Development
  National Environmental Research Laboratory
    Health Effects Research Laboratory

National Aeronautics and Space Administration

CONTENTS

CONTENTS (CONTINUED)

I. RECOMMENDATIONS FOR A KETONES STANDARD

NIOSH recommends that employee exposure to ketones in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of ketones on the health of employees and provide for their safety. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. Although NIOSH considers the workplace environmental limits to be safe levels based on current information, the employer should regard them as the upper boundaries of exposure and make every effort to maintain the exposure as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

These criteria and the recommended standard apply to exposure of employees in the workplace to acetone, (2-propanone), methyl ethyl ketone (2-butanone), methyl n-propyl ketone (2-pentanone), methyl n-butyl ketone (2-hexanone), methyl n-amyl ketone (2-heptanone), methyl isobutyl ketone (4-methyl-2-pentanone), methyl isoamyl ketone (5-methyl-2-hexanone), diisobutyl ketone (2,6-dimethyl-4-heptanone), cyclohexanone, mesityl oxide (4-methyl-3-penten-2-one), diacetone alcohol (4-hydroxy-4-methyl-2-pentanone), and isophorone (3,5,5-trimethyl-2-cyclohexan-1-one), referred to as "ketones" in this document.

Ketones have many industrial uses as chemical intermediates, solvents, and components in formulations, including inks, adhesives, and dyes. Exposure to ketones can cause local effects (irritation of eyes, upper respiratory tract, and skin) and systemic effects, the most important of which is peripheral neuropathy from methyl n-butyl ketone.

The action level is defined as half the time-weighted average (TWA) concentration environmental limit of each ketone. "Occupational exposure to ketones" is defined as exposure to ketones at a TWA concentration greater than the action level. Exposure at lower concentrations will not require adherence to the following sections, except for Sections 3(a), 4, 5, 6(b-e), 7, and 8(a).

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to ketones shall be controlled so that employees are not exposed at concentrations greater than the limits, in milligrams per cubic meter (mg/cu m) of air, in Table I-1 as TWA concentrations for up to a 10-hour workshift, 40-hour workweek.

(b) Sampling and Analysis

Workroom air samples shall be collected and analyzed for ketones by the methods described in Appendix I or by methods that are at least equivalent in precision, sensitivity, and accuracy.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all workers occupationally exposed to ketones.

TABLE I-1

RECOMMENDED EXPOSURE LIMITS FOR THE KETONES

Ketone	TWA Concentration Limits	
	mg/cu m	Approximate ppm equivalents
Acetone	590	250
Methyl ethyl ketone	590	200
Methyl n-propyl ketone	530	150
Methyl n-butyl ketone	4	1
Methyl n-amyl ketone	465	100
Methyl isobutyl ketone	200	50
Methyl isoamyl ketone	230	50
Diisobutyl ketone	140	25
Cyclohexanone	100	25
Mesityl oxide	40	10
Diacetone alcohol	240	50
Isophorone	23	4

(a) Preplacement examinations shall include at least:

(1) Comprehensive medical and work histories with special emphasis directed toward disorders of the nervous system, the respiratory system, and the eyes.

(2) Physical examination giving particular attention to the central and peripheral nervous systems, the respiratory system, and the eyes.

(3) Urinalysis, as an indicator of kidney function. In addition, appropriate tests for liver function should be considered by the responsible physician. For workers occupationally exposed to methyl n-butyl ketone, an electrodiagnostic examination including electromyography and nerve conduction velocity measurements shall be provided.

(4) A judgment of the worker's ability to use positive and negative pressure respirators.

(b) Periodic examinations shall be made available annually or more frequently when considered necessary by the responsible physician. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as outlined in paragraphs (a)(2) and (a)(3) of this section.

(c) During examinations, applicants or employees found to have medical conditions that might be directly or indirectly aggravated by exposure to ketones, for example, a case of preexisting neuropathy in the case of methyl n-butyl ketone, shall be counseled on the increased risk of impairment of their health by working with these substances.

In addition, employees who are occupationally exposed to methyl n-butyl ketone shall be made aware that repeated exposure can produce adverse effects on the nervous system and that accompanying signs and symptoms are insidious. If indicated by the electrodiagnostic examinations on those workers with occupational exposure to methyl n-butyl ketone, a neurologic consultation should be obtained, particularly in the presence of suspected neurologic abnormalities on preemployment or interim examination.

(d) Appropriate medical management shall be made available to those workers who suffer effects from exposure to ketones.

(e) Pertinent medical records shall be maintained for all employees occupationally exposed to ketones in the workplace. Records of environmental exposures applicable to an employee shall be included in that employee's medical records. Such records shall be kept for at least 30 years after termination of employment. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read the labels and signs provided shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs. Because acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, and mesityl oxide are flammable while methyl n-amyl ketone, diisobutyl ketone, methyl isoamyl

ketone, cyclohexanone, diacetone alcohol, and isophorone are combustible, all labels and warning signs shall bear the appropriate designation.

(a) Containers

Shipping and storage vessels containing ketones shall carry, in a readily visible location, the following pertinent label that bears the name of the specific ketones contained therein, the trade name of the product, if appropriate, and information on the effects of exposure to the compound on human health in addition to, or in combination with, labels required by other statutes, regulations, or ordinances. The information shall be arranged as in the following examples:

(1) Label for methyl n-butyl ketone:

METHYL N-BUTYL KETONE
(TRADE NAME)
FLAMMABLE
MAY CAUSE NERVE DAMAGE
IF INHALED, SWALLOWED, OR
ABSORBED THROUGH SKIN

Keep away from heat, sparks, and open flames.
In case of fire, use foam, dry chemical, or carbon dioxide fire extinguisher.
Avoid breathing vapor.
Do not get on skin, in eyes or mouth, or on clothing.
Keep containers closed when not in use.
Use only with adequate ventilation.

First Aid: If substance contacts skin, immediately wash affected area with soap and water. In case of eye contact, flush eye with copious amounts of running water. If overexposure should occur, consult a physician.

(2) Label for the other 11 ketones:

NAME OF KETONE
(TRADE NAME)

FLAMMABLE! (or: COMBUSTIBLE!)

HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

Keep away from heat, sparks, and open flames.
In case of fire, use foam, dry chemical, or carbon dioxide fire extinguisher.
Avoid breathing vapor.
Do not get on skin, in eyes or mouth, or on clothing.
Keep containers closed when not in use.
Use only with adequate ventilation.

First Aid: If substance contacts skin, immediately wash affected area with soap and water. In case of eye contact, flush eye with copious amounts of running water. If overexposure should occur, consult a physician.

(b) Work Area

Warning placards shall be affixed in readily visible locations in or near areas of occupational exposure to ketones. The information shall be arranged as in the following examples:

(1) Warning placard for methyl n-butyl ketone:

HAZARDOUS AREA
METHYL n-BUTYL KETONE
(TRADE NAME)
FLAMMABLE
MAY CAUSE NERVE DAMAGE
IF INHALED, SWALLOWED, OR
ABSORBED THROUGH SKIN

Prevent sources of heat, sparks, or open flames.
No smoking permitted. In case of fire use fire extinguishers at (location). Avoid breathing vapor.
Avoid contact with skin, eyes, and clothing.

(2) Warning placard for the other 11 ketones:

HAZARDOUS AREA
NAME OF KETONE
(TRADE NAME)
FLAMMABLE! (or: COMBUSTIBLE!)
HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

Prevent sources of heat, sparks, or open flames. No smoking or eating. In case of fire, use fire extinguishers at (location). Avoid breathing vapor. Avoid contact with skin, eyes, and clothing.

(3) Respiratory Protection

If respiratory protection is required in accordance with Section 4, the following statement in large letters shall be added to the required sign:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

Section 4 - Personal Protective Equipment and Clothing

(a) Respiratory Protection

The employer shall use engineering controls when needed to keep concentrations of airborne ketones at or below the recommended environmental limits. Compliance with this standard by the use of respirators is permitted only during installation and testing of engineering controls, during performance of nonroutine maintenance or repair, or during emergencies. When use of a respirator is permitted, it shall be selected and used in accordance with the following requirements:

(1) To determine the type of respirators to be used, the employer shall measure the concentration of airborne ketones in the workplace initially and thereafter whenever control, process, operational, worksite, or climatic changes occur that are likely to increase the concentration of airborne ketones.

(2) The employer shall ensure that no employee is exposed to ketones at concentrations above the recommended limits because of improper respirator selection, fit, use, or maintenance.

(3) A respiratory protection program shall be established. Requirements are found in 29 CFR 1910.134.

(4) The employer shall provide respirators in accordance with Table I-2 and shall ensure that the employees use the respirators properly when they are required. Respiratory protective devices shall be those approved by NIOSH and the Mine Safety and Health Administration.

(5) Respirators specified for use in higher concentrations of a specific airborne ketone may be used in an atmosphere of the same ketone at lower concentrations.

(6) The employer shall ensure that employees are properly instructed in the use of respirators assigned to them and in ways to test for leakage, proper fit, and proper operation.

(b) Protective Clothing

The employer shall provide appropriate protective clothing to employees who may have skin contact with liquid ketones. Protective clothing, including aprons, coats or coveralls, gloves, and boots, shall be made of material resistant to penetration by ketones. The employer shall ensure that personal protective clothing is regularly inspected for defects

TABLE I-2

RESPIRATOR SELECTION GUIDE FOR KETONES*

Ketone	Multiples of TWA Concentration Limit				Emergency Entry	Fire-fighting
	Less Than or Equal to			Greater Than		
	10X	50X	100X	100X		
Acetone	CDFHIJ	KL	KL	KL	KL	CK
Methyl n-butyl ketone	ABEG	CDFJ	HI	KL	KL	K
Methyl ethyl and methyl n-propyl ketone	B	CDFJ HI	KL	KL	KL	K
Other eight ketones**	B	CDFJ	HI	KL	KL	K

*See Respirator Code on the following page

** Methyl n-amyl ketone, methyl isobutyl ketone, methyl isoamyl ketone, diisobutyl ketone, cyclohexanone, mesityl oxide, diacetone alcohol, or isophorone

RESPIRATOR CODE

Code	Respirator Type Approved under Provisions of 30 CFR 11
A	Chemical cartridge respirator with half-mask facepiece and organic vapor cartridge
B	Chemical cartridge respirator with full facepiece and organic vapor cartridge
C	Gas mask with full facepiece and chin-type organic vapor canister
D	Gas mask with full facepiece and back- or front-mounted organic vapor canister
E	Type C supplied-air respirator, with half-mask facepiece, operated in demand (negative pressure) mode
F	Type C supplied-air respirator, with full facepiece, operated in demand (negative pressure) mode
G	Type C supplied-air respirator, with half-mask facepiece, operated in continuous-flow or pressure-demand mode
H	Type C supplied-air respirator, with full facepiece, operated in continuous-flow or pressure-demand mode
I	Type C supplied-air respirator with hood, helmet, or suit
J	Self-contained breathing apparatus, with full facepiece, operated in demand (negative pressure) mode
K	Self-contained breathing apparatus, with full facepiece, operated in pressure-demand or other positive pressure mode
L	Combination Type C supplied-air respirator, with full facepiece, operated in pressure-demand mode and equipped with auxiliary positive pressure self-contained air supply

and that it is worn by employees when necessary to prevent skin contact with liquid ketones.

(c) Eye Protection

The employer shall provide chemical safety goggles or face shields (20-cm minimum) with goggles and ensure that they are worn by employees where eye contact with liquid ketones is likely. Regulations concerning the selection, use, design, cleaning, limitations, precautions, and maintenance of eye protection equipment appear in 29 CFR 1910.133.

Section 5 - Informing Employees of Hazards from Ketones

(a) All new and current employees working with ketones shall be informed of the hazards, relevant signs and symptoms of overexposure, appropriate emergency procedures, including first aid, and proper conditions and precautions concerning safe use and handling of these compounds. Employees shall be informed, preferably by medical personnel, that ketones can irritate the eyes, nose, and throat and may cause impaired judgment at unknown concentrations and narcosis at high concentrations.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training, to ensure that all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator use. The instructional program shall include a description of the general nature of the environmental and medical surveillance procedures and of the advantage to the employees of participating in these surveillance procedures. As a minimum, instruction shall include the information in Appendix II, which shall be kept on file

and shall be readily accessible to employees at all places of employment where ketones are present.

(c) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix II or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Control of Airborne Ketones

Engineering controls, such as process enclosure or local exhaust ventilation, shall be used when needed to keep exposures to ketones at or below the permissible exposure limits. Ventilation systems, if used, shall be designed to limit accumulation or recirculation of ketones in the workplace environment. Exhaust ventilation systems discharging to outside air must conform to applicable local, state, and Federal air pollution regulations and must not constitute a hazard to employees or to the general population. Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by airflow measurements taken at least every 3 months. Motors in the exhaust systems shall be explosion proof, and all moving parts shall be made of nonsparking materials.

(b) Confined Spaces

Entry into and work in confined spaces, such as tanks, pits, vessels, or tank cars, that may contain ketones shall be controlled by adherence to the following requirements (or their equivalent).

(1) Before entering a confined space an employee shall obtain a permit. Permits shall be signed by an authorized representative

of the employer and shall certify that proper preventive and protective measures have been followed.

(2) Confined spaces that have contained ketones shall be cleaned with water and purged with air. Confined spaces should be isolated by locking out associated valves and switches to prevent accidental entry of ketones. They shall be tested to ensure that there is an adequate supply of oxygen and to ensure that ketones and other contaminants are not present in unsafe amounts and concentrations. Adequate ventilation shall be maintained while employees are in the confined space.

(3) An employee entering a confined space shall be furnished with appropriate personal protective equipment and shall be connected by a lifeline harness to another worker outside, who shall also be equipped for entry with approved personal protective equipment and have contact with a third party. The standby person shall keep in communication with the person in the confined space. The third person, equipped to aid the other two if necessary, shall observe their activities.

(c) Storage and Handling

(1) Containers of ketones shall be kept tightly closed at all times when not in use. They shall be of a type designed to contain flammable or combustible liquids and shall be stored safely to minimize the possibility of breaks, spills, or leaks. Ketones shall be kept away from excessive heat, sparks, and flames.

(2) Employers shall ensure that improperly informed, trained, and equipped personnel are not involved in storing, loading, unloading, or processing ketones.

(3) Guidelines and regulations on the storage and handling of flammable and combustible liquids are found in 29 CFR 1910.106.

(d) Cleanup and Waste Disposal

(1) Spills of liquid ketones shall be cleaned up promptly and in a manner that will minimize the inhalation of, skin contact with, and hazard of fire from the ketones.

(2) Rags, mops, and other materials contaminated with ketones shall be stored in closed metal containers.

(3) Waste material containing ketones shall be disposed of in a manner that is not hazardous to employees or to the general population and that conforms to applicable local, state, and Federal regulations.

(e) Emergency Procedures

(1) The employer shall formulate emergency evacuation, medical, and firefighting procedures and shall ensure that employees are instructed in these procedures and that the instructions are posted in all work areas where emergencies such as large spills involving ketones might occur. Emergency procedures shall include prearranged plans for immediate evacuation, transportation, and medical assistance for affected employees, including alerting designated medical facilities to the impending arrival of affected workers.

(2) Necessary emergency equipment, including respirators, shall be available in readily accessible locations, and employees shall be instructed in its use.

(3) Employees not essential to emergency operations shall be evacuated from hazardous areas during emergencies. The perimeters of these areas shall be delineated, posted, and secured. Employers shall

ensure that personnel who are not trained in emergency procedures and protected against the attendant hazards do not shut off sources of ketones, clean up spills, control and repair leaks, and fight fires where ketones are present.

(4) Employers shall provide emergency drench showers, eyewash fountains, and washroom facilities that are readily accessible to workers in all areas where skin or eye contact with liquid ketones is likely. If liquid ketones are splashed on the clothing or skin, contaminated clothing and shoes shall be promptly removed and the skin washed thoroughly with soap and water. If liquid ketones get into the eyes, the affected area shall be irrigated immediately with copious quantities of running water.

(5) The employer shall ensure, through regularly scheduled inspection and maintenance, that all emergency equipment, including washing facilities, is in proper working order.

Section 7 - Sanitation

(a) Regulations concerning plant sanitation are found in 29 CFR 1910.141.

(b) The employer shall provide appropriate changing and shower rooms. Requirements for such rooms are found in 29 CFR 1910.141(e).

(c) Clothing that has been contaminated by ketones shall be discarded or decontaminated by laundering or drying under an exhaust hood or by an equivalent method.

(d) The employer shall inform persons involved in laundering or otherwise handling clothing or equipment contaminated with ketones of the potential hazards of exposure to ketones.

(e) Employers shall prohibit the use of ketones for handwashing and other personal cleaning purposes.

(f) Employees who handle ketones shall be instructed by their employer to wash their hands thoroughly with soap and water before using toilet facilities, eating, or smoking.

Section 8 - Monitoring and Recordkeeping Requirements

(a) Each employer with a place of employment where ketones are manufactured, processed, stored, used, handled, or otherwise present shall determine by an industrial hygiene survey if there is occupational exposure to ketones. Records of these surveys, including the basis for concluding that there is no occupational exposure to ketones, shall be maintained. Surveys shall be repeated at least annually and within 30 days of any change likely to alter concentrations of any of these compounds in the workplace air.

(b) If it is determined that there is occupational exposure to ketones, the employer shall fulfill the following requirements:

(1) A program of personal monitoring shall be instituted to identify and measure, or to permit calculation of, the exposure of each employee occupationally exposed to airborne ketones. Source and area monitoring may be used to supplement personal monitoring.

(2) In all personal monitoring, samples representative of the breathing zones of the employees shall be collected.

(3) For each TWA concentration determination, a sufficient number of samples shall be taken to characterize the employees' exposures during each workshift. Variations in work and production schedules and in employees' locations and job functions shall be considered in choosing sampling times, locations, and frequencies.

(4) Each operation in each work area shall be evaluated at least every 3 months if it is determined that there is occupational exposure.

(5) If an employee is found to be exposed to ketones in excess of any of the TWA concentration limits specified in Section 1a, the exposure of that employee shall be measured at least once a week, control measures shall be initiated, and the employee shall be notified of the extent of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, 1 week apart, indicate that the employee's exposure no longer exceeds the appropriate limits. Routine monitoring may then be resumed.

(c) Recordkeeping

Records of workplace environmental monitoring shall be kept for at least 30 years after the employee's last occupational exposure to ketones. These records shall include the dates and times of measurements, job function and location of the employee within the worksite, methods of sampling and analysis used, types of respiratory protection in use at the time of sampling, TWA concentrations found, and identification of the exposed employee. Employees shall be able to obtain information on their own workplace environmental exposures. Workplace environmental monitoring

records shall be made available to designated representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare.

Pertinent medical records shall be retained by the employer for 30 years after termination of employment. Records of environmental exposures applicable to an employee should be included in medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing impairment of health from workplace exposure to ketones. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. Criteria for a recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments, and simply complying with the recommended standard should not be regarded as the final goal.

These criteria for a standard for ketones are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to workplace exposure to ketones arising from the processing, manufacture, and use of these ketones. The standard is not designed for the population-at-large, and any extrapolation beyond the occupational environment is not warranted. It is intended to (1) protect against injury from ketones, (2)

be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (3) be attainable with existing technology.

There are a number of areas that need further research with respect to ketones. The possibilities of carcinogenic, mutagenic, teratogenic, and reproductive effects from ketones have not been thoroughly investigated. Epidemiologic studies on all of the ketones are also needed. Furthermore, toxicologic information from repeated exposures of experimental animals is deficient for most of the ketones. Animal experiments are needed to determine if ketones other than methyl n-butyl ketone produce peripheral neuropathy. The effects of various mixtures of the ketones and interactions that may occur have not been studied. Research in this complex area is needed. Pharmacokinetic studies (absorption, distribution, metabolism, and excretion) are also needed to help investigators understand the mechanism of action of ketones on the nervous system.

Exposure to ketones in the workplace is a major concern because one of these compounds has caused a neurologic disorder, and all of them may cause irritation of the eyes, nose, and throat, impaired judgment, and narcosis in humans. Exposure occurs primarily when ketones are inhaled or absorbed through the skin.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Ketones are compounds with a carbonyl group, C=O, which is attached to two carbon atoms. They are represented by the general formula RCOR' [1]. The 12 ketones discussed in this document are acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, methyl n-amyl ketone, methyl isobutyl ketone, methyl isoamyl ketone, diisobutyl ketone, cyclohexanone, mesityl oxide, diacetone alcohol, and isophorone. These ketones are known by a number of synonyms, some of which are listed, along with chemical and structural formulas of the compounds, in Table XI-1. Important physical and chemical properties are presented in Table XI-2.

Some of the applications of these ketones in industry are determined by the solvent properties, rate of evaporation, boiling point, viscosity, and availability [2]. Ketones are used as chemical intermediates in chemical manufacturing industries; as solvents for natural and synthetic resins in coating industries; as components in formulations such as inks, adhesives, and dyes; as extraction agents for lubricating oil; in wax refining; and for rare metal flotation in refining processes [1,3]. A list of occupations in which there is potential exposure to these ketones is presented in Table XI-3.

(a) Acetone

Acetone, CH_3COCH_3, is a colorless, highly volatile, flammable liquid with a burning taste and aromatic odor [4]. It is the simplest but most commercially important ketone [5]. Acetone occurs normally in small amounts in human blood and urine [6].

Commercially, acetone is produced by catalytic dehydrogenation of isopropyl alcohol or by oxidation of cumene [5]. Before World War I, small amounts of acetone were produced from the dry distillation of wood. In the mid-1920's, most acetone was manufactured by the dehydrogenation of isopropyl alcohol.

In 1976, about 1,922 million pounds of acetone were produced in the United States [7]. About 58% of the acetone produced in the United States and Puerto Rico was manufactured by oxidizing cumene, and the remaining 42% was made by dehydrogenating isopropyl alcohol [8]. About 25% of the acetone produced was used to make methyl methacrylate, 13% to make methyl isobutyl ketone, 10% as a solvent for protective coatings, and the rest was used in manufacturing diacetone alcohol, methyl isobutyl carbinol, isophorone, mesityl oxide, higher methacrylates, bisphenol A, and other chemicals [8].

In addition to being used as a chemical intermediate, acetone is an excellent solvent for many natural gums and resins, for cellulose derivatives such as nitrocellulose, cellulose esters, and ethyl cellulose, and for synthetic resins such as vinyl and modified phenolic types, alkyds, and methacrylates [5]. Acetone is also used as a solvent in manufacturing smokeless powder, cements, and artificial leather.

NIOSH estimates that 2,816,000 workers are potentially exposed to acetone in the United States.

(b) Methyl Ethyl Ketone

Methyl ethyl ketone, CH3COCH2CH3, is a colorless liquid with an acetone-like odor and is produced commercially either by dehydrogenation or selective oxidation of sec-butyl alcohol [1]. In 1976, about 524 million

pounds of methyl ethyl ketone were produced in the United States [7].

Methyl ethyl ketone is mainly used as a solvent for formulations of nitrocellulose [1]. It is also used in the manufacture of synthetic surface coatings made from acrylic resins, vinyl acetates, cellulose acetate-butyrate, ethyl cellulose, and vinyl chloride-vinyl acetate copolymers. Methyl ethyl ketone is used as a dewaxing solvent in the refining of lubricating oils. It is used to manufacture methyl isopropenyl ketone, sec-butyl amine, and 1,3-diketones.

NIOSH estimates that 3,031,000 workers are potentially exposed to methyl ethyl ketone in the United States.

(c) Methyl n-Propyl Ketone

Methyl n-propyl ketone, $CH_3(CH_2)_2COCH_3$, is a clear liquid with a strong odor resembling that of acetone but having a more ethereal character [9]. It is made primarily by the oxidation of 2-pentanol. Methyl n-propyl ketone is used as a solvent, either alone or in combination with other solvents.

NIOSH estimates that fewer than 500 workers are potentially exposed to methyl n-propyl ketone in the United States.

(d) Methyl n-Butyl Ketone

Methyl n-butyl ketone, $CH_3CO(CH_2)_3CH_3$, is a colorless liquid with a strong odor resembling that of acetone but more pungent [9]. Commercially, it is produced by the catalyzed reaction of acetic acid and ethylene under pressure.

Methyl n-butyl ketone is used in the lacquer industry as a solvent for lacquers and in lacquer and varnish removers [9]. It is a useful solvent for nitrocellulose, resins, oils, fats, and waxes.

NIOSH estimates that 222,000 workers are potentially exposed to methyl n-butyl ketone in the United States.

(e) Methyl n-Amyl Ketone

Methyl n-amyl ketone, CH3CO(CH2)4CH3, is a liquid with marked fruity odor [9]. It occurs naturally in oil of cloves and in Ceylon cinnamon oil [1]. Commercially, it is produced primarily by the catalytic dehydrogenation of 2-heptanol [9]. It is a useful solvent in synthetic resin finishes, particularly for metal roll coating [1].

NIOSH estimates that 67,000 workers are potentially exposed to methyl n-amyl ketone in the United States.

(f) Methyl Isobutyl Ketone

Methyl isobutyl ketone, CH3COCH2CH(CH3)2, is a colorless liquid with a pleasant odor [9]. It is manufactured commercially by the selective catalytic hydrogenation of the double bond in mesityl oxide.

Methyl isobutyl ketone is used as a solvent in synthetic resinous paints, lacquers, and varnishes [10]. It is also used as a solvent for adhesives, rubber cements, aircraft dopes with cellulose acetate-butyrate bases, 2,4-D, and DDT [1]. As an extractant, methyl isobutyl ketone is used in dewaxing mineral oils, refining tall oil, and cleaning metals [1]. In the recovery of uranium from fission products, methyl isobutyl ketone is used in the solvent extraction process [3].

NIOSH estimates that 1,853,000 workers are potentially exposed to methyl isobutyl ketone.

(g) Methyl Isoamyl Ketone

Methyl isoamyl ketone, CH3CO(CH2)2CH(CH3)2, is a colorless, stable liquid with a pleasant odor. It is used as a solvent for nitrocellulose, cellulose acetate, and acrylic and vinyl copolymers [11]. NIOSH estimates that 19,000 workers in the United States are potentially exposed to methyl isoamyl ketone.

(h) Diisobutyl Ketone

Diisobutyl ketone, (CH3)2CHCH2COCH2CH(CH3)2, is an oily liquid of low volatility with a peppermint odor [1]. Commercially, diisobutyl ketone is produced by the reduction of phorone or as a byproduct in the manufacture of methyl isobutyl ketone from acetone [1].

It is used as a solvent for nitrocellulose, milled crepe rubber, vinylite, and synthetic coatings [9] and as a dispersant for organosol-type resins. It is also used in the synthesis of inhibitors, dyes, pharmaceuticals, and insecticides [9]. It is useful as a dewaxing agent for lubricating oils [1].

An estimate of the number of workers who are potentially exposed to diisobutyl ketone in the United States is not available.

(i) Cyclohexanone

Cyclohexanone, C6H10O, is a colorless liquid with an odor suggestive of peppermint [12]. Cyclohexanone can be produced by the catalytic air oxidation of cyclohexane, by the catalytic dehydrogenation of cyclohexanol, or by the oxidation of cyclohexanol. The most common method probably is catalytic air oxidation of cyclohexane, which produces a mixture of cyclohexanol and cyclohexanone.

In 1975, about 554 million pounds of cyclohexanone were produced in the United States [13]. Its most commercially important use is as a chemical intermediate in the manufacture of adipic acid [3]. In lacquer industries, cyclohexanone is used as a solvent and thinner for lacquers that contain nitrocellulose or vinyl chloride polymers and copolymers [12]. It is used as a solvent for many resins, including vinyls, cellulose esters, ethyl cellulose, polystyrene, acrylics, and crude rubber [3]. It is also used in stain, spot, and paint removers, metal degreasers, adhesives, polishes, and lube oil [3].

NIOSH estimates that in the United States there are 1,190,000 workers potentially exposed to cyclohexanone.

(j) Mesityl Oxide

Mesityl oxide, $CH_3COCH=C(CH_3)_2$, is a colorless liquid with a strong odor of peppermint [9]. It is produced commercially by dehydration of diacetone alcohol or by autoxidation of acetone [1].

In 1975, approximately 46 million pounds of mesityl oxide were produced in the United States [14]. Mesityl oxide is used as a solvent for nitrocellulose, vinyl chloride-vinyl acetate copolymers, synthetic rubbers, gums, resins, and ink pastes [1]. It is found in paint and varnish removers, carburetor cleaners, stain removers, and flotation agents. It is also used to produce lubricating oil additives, plasticizers, and methyl isobutyl ketone [1].

NIOSH estimates that in the United States fewer than 500 workers are potentially exposed to mesityl oxide.

(k) Diacetone Alcohol

Diacetone alcohol, CH3COCH2C(CH3)2OH, is a colorless liquid with a pleasant, minty odor [1,2]. It is usually prepared by the aldol condensation of acetone with an alkaline catalyst [1].

Diacetone alcohol is an excellent solvent for cellulose acetate, nitrocellulose, vinyl chloride-vinyl acetate resins, and epoxy resins [1]. The pure (acetone-free) form is a component of castor oil-based hydraulic brake fluids. It also has numerous applications in the tanning industry [2].

NIOSH estimates that 1,350,000 workers are potentially exposed to diacetone alcohol in the United States.

(l) Isophorone

Isophorone, C9H14O, is a high-boiling (215.2 C), colorless liquid of low volatility with an odor resembling peppermint [9]. It is produced commercially by either of two methods, both of which require acetone as an intermediate. Acetone is passed over calcium oxide, hydroxide, carbide, or a mixture of these at 350 C, or it is heated at 200-250 C under pressure. Isophorone is used as a solvent for oils, fats, gums, and natural and synthetic resins and as a chemical intermediate.

NIOSH estimates that 1,507,000 workers are potentially exposed to isophorone in the United States.

Effects on Humans

(a) Sensory Effects

A number of investigators have studied the irritating effects of ketones in humans. In 1943, Nelson et al [15] reported on the sensory

thresholds of ACETONE, METHYL ETHYL KETONE, and CYCLOHEXANONE in a study designed to determine comfortable working concentrations for these ketones. Concentrations were nominal, ie, they were calculated from weight loss in a bubbler or from dropping the ketone at a known rate onto a hot plate. An average of 10 men and women were exposed to each ketone at various concentrations for 3-5 minutes. In some studies, the experimenters themselves served as subjects. Each individual classified the effects on the eyes, nose, and throat as very irritating, slightly irritating, or causing no reaction. The odor was classified as absent, definite, moderate, strong, or overpowering. Finally, the subjects were asked to estimate if they could work for 8 hours in an atmosphere of the ketone at each given concentration. The concentration of the ketone that most subjects rejected as a working atmosphere was termed objectionable, and the next lower concentration tested was proposed as a tentative practical limit. In a similar study from the same laboratory published in 1946, Silverman et al [16] reported on the sensory thresholds for METHYL ISOBUTYL KETONE, DIISOBUTYL KETONE, MESITYL OXIDE, DIACETONE ALCOHOL, and ISOPHORONE. The experimental design was the same as that used by Nelson et al [15], except that an average of 12 men and women were exposed to the ketones for 15 minutes [16]. The results of these two studies are summarized in Table III-1.

For acetone, some irritation was reported at 300 ppm (711 mg/cu m), and methyl ethyl ketone produced mild eye irritation in some subjects at 200 ppm (588 mg/cu m) and slight nose and throat irritation at 100 ppm (294 mg/cu m) [15]. Nelson et al noted that methyl ethyl ketone at 300 ppm (882 mg/cu m) was objectionable, although this was below the concentration at

TABLE III-1

SENSORY THRESHOLDS IN HUMANS FOR KETONES

Ketone	Highest Satisfactory Concentration* (ppm)	Irritating Concentration** (ppm)			Reference
		Eyes	Nose	Throat	
Acetone	200	500	500	500	15
Methyl ethyl ketone	200	350	350	350	15
Methyl isobutyl ketone	100	200	>200	>200	16
Diisobutyl ketone	25	50	>50	>50	16
Cyclohexanone	25	75	75	75	15
Mesityl oxide	25	25	50	>50	16
Diacetone alcohol	50	100	>100	100	16
Isophorone	10	25	25	25	16

*Concentration judged by majority of exposed volunteers to be satisfactory for an 8-hr exposure
**Concentration that caused irritation in the majority of subjects

which a majority of subjects experienced irritation. Most subjects considered methyl isobutyl ketone to have an objectionable odor at 200 ppm (820 mg/cu m), diisobutyl ketone above 25 ppm (145 mg/cu m), mesityl oxide above 50 ppm (201 mg/cu m), diacetone alcohol at 100 ppm (474 mg/cu m), and isophorone at 25 ppm (141 mg/cu m) [16]. After exposure to mesityl oxide, many subjects reported an unpleasant taste lasting 3-6 hours; subjects also noted an unpleasant taste from diacetone alcohol.

These sensory threshold studies [15,16] have certain shortcomings. The concentrations of ketones in the exposure chamber were calculated (nominal) rather than measured analytically, so the true concentration may have been lower than those reported. In the study by Nelson et al [15], the use of the experimenters as subjects was a possible source of bias, and the exposure periods of 3-5 minutes were not long enough to show if adaptation would occur. The 15-minute exposures used by Silverman et al [16] should have permitted a more accurate observation of olfactory fatigue and a better appraisal of increasing or decreasing irritation with continued exposure, but the authors did not discuss possible acclimatization. The fact that exposure duration did not approach that of a normal workshift is the major limitation of these studies. However, the data are useful as a guide to the relative irritating properties of ketones and the concentrations at which these appear.

Raleigh and McGee [17] investigated the effects on workers of exposure to acetone at high concentrations. Air samples from the workroom and the workers' breathing zones were collected in plastic bags at random times during the workshift. Breath samples from the workers were collected at end-expiration before, during, and after each workshift. All air samples were analyzed by gas-liquid chromatographic methods.

In July 1968 [17], nine workers were examined daily for 7 consecutive 8-hour workdays. Air samples were collected, and symptoms, such as headache, drowsiness, dizziness, nausea, or irritation of the eyes, nose, or throat, were looked for. A brief physical examination paid particular attention to the eyes, nose, and throat and to central nervous system (CNS) effects (gait, finger to nose test, and Romberg's sign). Average 8-hour

daily exposure concentrations for the workers were 1,006 ppm (2,386 mg/cu m, range 950-1,060 ppm; 2,252-2,386 mg/cu m). Breath samples showed a range of 1-420 ppm (2-995 mg/cu m) during the day, with a morning average of 56 ppm (133 mg/cu m) and an afternoon average of 221 ppm (524 mg/cu m). Eye irritation was reported by seven of the nine employees, with three of them reporting eye irritation more than once. Four complained of throat irritation, three of headache, three of lightheadedness, and two of nasal irritation, with one reporting nasal irritation twice. The authors said that these symptoms were intermittent and transient and that they occurred when the concentrations of airborne acetone were considerably higher than 1,000 ppm (2,370 mg/cu m). However, four workers had slight to mild irritation at 800-1,000 ppm (1,896-2,370 mg/cu m). On physical examination, one worker had a slight redness of the nasal mucous membranes, and one had slight congestion of the mucosa of the nose and throat. The authors concluded that there was no indication of CNS disorders.

In 1972, Raleigh and McGee [17] conducted an additional study of two men for three 8-hour shifts and two men for two 8-hour shifts. Physical examinations similar to those in the 1968 study were performed and the workers were also given a psychomotor test, but this test was subsequently shown to be unreliable in measuring psychomotor impairment from alcohol intoxication. Environmental samples contained essentially the same concentration of acetone as those in the first part of this study. Breath samples also showed a similar range of acetone concentrations; however, the concentration was considerably lower (20 ppm; 474 mg/cu m) in the morning than those taken from workers examined previously. Two of the four workers complained of eye irritation, with one reporting the irritation on two

occasions. One of the workers complained of throat irritation, and three noted nasal irritation. On physical examination, one employee had a slight throat congestion.

A correlation of odor threshold and eye irritation with exposure concentration was reported [17]. Most reports of odor detection occurred when the concentration of acetone was near or above 1,000 ppm (2,370 mg/cu m). Of 31 air samples in the 1968 study that were correlated with complaints of eye irritation, 10 were reported to contain acetone at 1,000-1,500 ppm, while the other incidents of eye irritation occurred above 1,500 ppm (3,555 mg/cu m). One individual showed a variable response, noting discomfort several times at concentrations between 1,042 and 6,053 ppm (2,470 and 14,346 mg/cu m) but, on another occasion, he reported no eye irritation at a concentration of 6,596 ppm (15,632 mg/cu m), although he did experience some burning of the throat.

Raleigh and McGee [17] concluded from these experiments that 1,000 ppm was a safe concentration for acetone since they did not consider the slight irritation at 800-1,000 ppm to be cause for concern. They also indicated that the irritation seen at much higher concentrations was mild and transient and that no objective evidence was available from the physical examinations to support the symptoms of eye irritation reported by the workers.

Matsushita et al [18] conducted a study to determine the maximum permissible concentration of acetone. Twenty-five healthy male students, about 22 years old, were divided into five groups. Four groups were exposed to acetone at concentrations of 100, 250, 500, or 1,000 ppm (237,

592, 1,180, or 2,370 mg/cu m) for 6 hours, and the remaining group served as a control. Methods of generating vapor-air mixtures or of measuring concentrations of airborne acetone were not presented.

The authors [18] reported that the subjects recognized the smell of acetone at all exposure concentrations, but that they seemed to get used to the smell. Most of the subjects exposed at 500 or 1,000 ppm had irritation of the nose, eyes, throat, and trachea. Only a few in the other groups had irritation.

In the groups exposed at 500 and 1,000 ppm, there were complaints of tension, general weakness, heavy eyes, or lack of energy the following morning. In the group exposed at 250 ppm, there were fewer complaints of the same nature. None of the volunteers exposed at 100 ppm had any complaints.

Although no sampling and analytical procedures were described, this study suggests that exposure to acetone at concentrations below 1,000 ppm can cause irritation of the eyes, nose, and throat.

In a 1935 report of an animal study, Patty et al [19] mentioned that men momentarily exposed to METHYL ETHYL KETONE at approximately 3.3 and 10% had intolerable irritation of the eyes and nose. Methyl ethyl ketone at 1% had a strong odor and was almost intolerable, while at 0.33% it had a moderate to strong odor and was moderately irritating to the eyes and nose.

In 1953, Carpenter et al [20] described the irritating effects of DIISOBUTYL KETONE in volunteers. Two men (25 and 32 years old) were exposed to diisobutyl ketone at 50 ppm (290 mg/cu m) for 3 hours in a 6.5-foot cube. Concentrations of airborne diisobutyl ketone were monitored by interferometry. The subjects recorded pulse rates and subjective symptoms

during the exposure. Both men had a transitory, slight irritation of the eyes and nose at the beginning of exposure [20]. They could smell and taste diisobutyl ketone throughout the exposure, but they reported no change in the taste of cigarettes smoked at the end of exposure. (Carpenter et al apparently thought smoking was a sensitive indicator of a nonspecific effect.) There was no significant change in pulse rate or blood pressure, and urine sugar and albumin tests 1 hour and 24 hours after exposure were negative. The two subjects estimated that a workplace atmosphere of diisobutyl ketone at 50 ppm would be satisfactory for an 8-hour exposure.

Ten days later, the same two men and another man, 43 years old, were similarly exposed to diisobutyl ketone at a concentration of 100 ppm (581 mg/cu m) for 3 hours [20]. Each subject drew six circles and six squares at the beginning, middle, and end of exposure. Initially, all three men experienced slight irritation of the eyes and nose. Diisobutyl ketone could be tasted by two subjects after 1 hour, and slight throat irritation was noted by one subject after 1.5 hours. Slight tearing occurred in one man, and the other two had slight headaches after 2 hours. After the exposure, two subjects felt slightly dizzy upon entering a fresh air atmosphere. The two men who smoked after the exposure complained of an unpleasant taste. Pulse rates, blood pressures, and the results of urinalyses were normal. Performance on the coordination tests was not affected by the vapor exposure. The subjects estimated that a workplace atmosphere of diisobutyl ketone at 100 ppm would be unsatisfactory. On the basis of comfort, the authors [20] recommended that workplace air should not contain diisobutyl ketone at concentrations higher than 50 ppm.

Smyth et al [21], in a report of animal toxicity, commented that MESITYL OXIDE had an objectionable odor to the investigators; however, they also pointed out that their dislike of the odor diminished rapidly with familiarity. This finding might indicate olfactory fatigue or adaptation to the odor.

(b) Systemic Effects

General systemic effects resulting from exposure to ACETONE and to METHYL ISOBUTYL KETONE have been described by several investigators. A 1903 report [22] described the death of a 12-year-old boy who lapsed into a state resembling a diabetic coma after a large celluloid dressing dampened with acetone had been applied.

In 1952, Harris and Jackson [23] described a case of acute ACETONE poisoning in a 10-year-old boy. He was exposed to acetone vapor at an unknown concentration in a warm room (about 82 F) while a lightweight hip cast was applied, reaching from nipple level to the right ankle, and including the left thigh. The cast consisted of glass and textile bandages set with a mixture of 90% acetone, 9% pentane, and 1% methyl salicylate.

About 8 hours after the cast was applied, the boy became restless, complained of a headache, and felt that the cast, although it fit loosely, was tight across his abdomen [23]. Approximately 4 hours later, he vomited, and persistent vomiting began 1.5 hours later. The patient became more restless, and, within 15 minutes, he collapsed. The cast was slit down the side but not removed. Eight hours after the original symptoms appeared, the boy was pale and almost stuporous. He continued to vomit, and his blood pressure was 80/60. His spontaneous speech was incoherent, although he could answer questions correctly. About 12 hours after the

original symptoms were noted, the cast was removed. The inside of the cast was wet and sticky and smelled of acetone. The skin that had been touching the cast was apparently unchanged.

An hour after the cast was removed, the patient fell into a deep sleep [23]. Three hours later, he was extremely ill and apathetic, and his respiration was rapid, deep, and irregular. His pulse rate was 132 and his blood pressure was 120/70. After taking a drink, he vomited a brownish material that gave a positive benzidine reaction, indicating that there was blood in the stomach. The urine contained acetone, diacetic acid, and sugar. The concentration of acetone in the blood about 6 hours after the cast had been removed was 15 mg/100 ml. (Normal values for acetone range from 0.3 to 2.0 mg/100 ml blood according to a table in Stedman's Medical Dictionary which probably lists values for adults [6]).

Supportive therapy consisting of intravenous (iv) administration of dextrose in saline was given following a presumptive diagnosis of acetone poisoning [23]. The patient's condition returned to almost normal after about 16 hours of therapy, although the smell of acetone on his breath was still noticeable. By the 4th day, his condition was normal, and no acetone was detected on his breath or in his urine.

Harris and Jackson [23] pointed out that they could not distinguish the relative amount of acetone absorbed through the lungs from that absorbed percutaneously. They stated that this patient had a habit of sleeping with his head under the covers, which would have increased the respiratory exposure. The authors thought skin absorption might have occurred, and they stated that previous work to determine skin absorption of acetone had not provided contact as extensive or as intimate as that

seen in this case. It is not clear whether the patient's illness was caused by skin absorption or inhalation of acetone or by both. One other study [24], however, described in detail a case where apparently less skin contact did not result in acetone absorption; this is discussed in more detail in Subsection (e) of this chapter. In addition, the possible contribution of pentane or methyl salicylate to this poisoning was not considered by the authors.

Ross [25] described adverse health effects in eight male workers, aged 30-57 years, who were exposed to acetone vapor. Four of them had been cleaning out a pit, 12 feet deep, in an enclosed building. Two 10-gallon tanks of acetone and two 10-gallon tanks of 1,1,1-trichloroethane were stored nearby. Draeger tube measurements in the pit, made 3 hours, 18 hours, and 1 week after the exposure, revealed acetone concentrations in excess of 12,000 ppm (28,440 mg/cu m) and 1,1,1-trichloroethane levels up to 50 ppm.

The workers in the pit noticed a "sweet sickly smell" and complained of throat and eye irritation, weakness of the legs, and headache during the morning shift [25]. After returning to work from lunch, one worker fainted, and several of the workers felt dizzy and lightheaded and reported weakness in the legs. One of the workers noted the dizziness and weakness after an exposure of 2 minutes. Urine samples from five of the eight workers taken 90 minutes after the original exposures showed acetone levels of 4.6-7.15 mg/100 ml of urine. Urine specimens taken from two other workers 45 hours after the episode showed a trace of acetone in one and 2.4 mg/100 ml in the other. Urine specimens collected from the eight workers 7 days after the exposure showed acetone concentrations ranging from 0.39 to

1.29 mg/100 ml. The diagnosis of "acute acetone intoxication" was made for these workers on the basis of their symptoms, urinary acetone concentrations, and environmental concentrations of airborne acetone. The authors did not consider the measured concentration of 1,1,1-trichloroethane (50 ppm) sufficient to cause adverse effects. Data presented by NIOSH in Criteria for a Recommended Standard....Occupational Exposure to 1,1,1-Trichloroethane (Methyl Chloroform) [26] are consistent with this conclusion. In that document NIOSH recommended an environmental limit of 350 ppm (1,910 mg/cu m) as a 15-minute ceiling. The effects observed in these workers indicate that acetone concentrations in excess of 12,000 ppm (28,440 mg/cu m) are an acute health hazard. The narcosis induced by acetone is cause for special concern, since it implies that exposure to acetone at lower concentrations may cause impaired judgment or other behavioral effects that could affect the health and safety of workers. These data, however, do not permit determination of a threshold value for judgmental impairment.

Parmeggiani and Sassi [27] investigated the effects of acetone in a collodion preparation department of a plant engaged in the production of cellulose acetate fibers. Eight workers had to dismantle a filter and replace the filter element, the two operations lasting about 3 hours. For the remainder of the day, these workers were not exposed to acetone. During removal, mounting, and changing of the filter, acetone concentrations ranged from 307 to 918 ppm (730 to 2,180 mg/cu m). The acetone concentration was determined following preliminary absorption in distilled water, apparently with an impinger. The specific method of analysis was not described. The temperature in the filter rooms was

maintained at 38-40 C (100-104 F). The authors examined the effects of acetone on seven of these workers, aged 19-53 years, who had been employed from 6 months to 13 years.

The first worker loaded the mixers, where acetone at a concentration of 25 ppm (60 mg/cu m) was found [27]. Examinations showed hyperemia of the conjunctiva and pharynx, rough breathing with some basal rhonchi, and slight choleduchol duodenal pain on palpation. He complained of asthenia, somnolence, occasional dizziness, and insomnia.

Of the other six workers who were exposed at 309-918 ppm, all complained of somnolence, four had eye and throat burning, two felt dizzy, and two felt inebriated, one had epigastric pain, one had a heavy head, and one complained of headaches [27]. The results of examination of one man were normal, but five had evidence of pharyngeal irritation, three had conjunctival irritation, and four had signs of lung irritation.

Although the authors [27] did not describe the method of analysis, and the temperature of the room may have contributed to the effects, this study does show that exposure to acetone at concentrations less than 1,000 ppm can cause harmful effects.

Parmeggiani and Sassi [27] also studied the elimination of acetone in workers. Based on a study in which acetone was administered orally to volunteers and then determined in the blood and breath, they were able to calculate a theoretical distribution ratio. Thus, in workers exposed to acetone for 3 hours at 833 ppm (2,000 mg/cu m), twice each shift with a 1-hour rest between exposures, the authors found an average concentration of 190 mg/liter at the end of work. They calculated that this corresponded to a blood acetone level of 85.5 mg/liter. Sixteen hours after the end of the

workshift, the concentration of acetone in the expired air declined to 32 μg/liter, which was equivalent to 14.5 mg/liter in the blood, according to the authors. In the opinion of the investigators, this was evidence that exposure to acetone at concentrations slightly less than the present Federal standard could lead to accumulation in the body. They added that, by the end of the weekend, ie, 48 hours after exposure, the acetone had disappeared.

Vigliani and Zurlo [28] discussed the health of factory workers who had been exposed to acetone at a concentration of 1,000 ppm (2,370 mg/cu m), 3 hours/day, for 7-15 years. These workers appeared to have been the same as those studied by Parmeggiani and Sassi [27], although the two reports differ in some details. All of the workers examined had inflammation of the respiratory tract, stomach, and duodenum and occasional dizziness and loss of strength. Similar effects were also reported in workers exposed at 700 ppm, (1,660 mg/cu m), but the authors did not specify whether this was a short- or long-term exposure. Exhaled air of workers exposed at 1,000 ppm for 3 hours/day at the end of the workshift contained 0.2 mg of acetone/liter and their urine contained 160 mg/liter. The next morning, acetone was detected at concentrations of 0.03 mg/liter in exhaled air and at 10 mg/liter in the urine. On Monday morning, no acetone was detected in exhaled air. The concentration of acetone in the urine at this time was not reported.

Gitelson et al [29] examined the development of clinical signs in a 42-year-old man who had ingested about 200 ml of acetone. An hour later, he was stuporous, with flushed cheeks, shallow respiration, and a regular pulse rate of 108. His temperature and blood pressure were normal, and,

although his abdominal reflexes were absent, he had normal tendon reflexes. His throat was red and swollen, and erosions were observed on the soft palate and around the entrance to the esophagus. His breath smelled strongly of acetone. His urine showed traces of albumin and a few hyaline casts and leukocytes but no sugar. It was strongly positive for acetone and acetoacetate.

The patient lapsed into a coma shortly after he was admitted to a hospital [29]. He was given supportive therapy and regained consciousness about 12 hours later. Six days later, he had pain when he moved his legs or hips, and he had hyperesthesia of the legs that gradually disappeared over 2 months.

Four weeks after ingesting the acetone, the man noticed an increased fluid intake and urine output [29]. An oral glucose tolerance test 2.5 months after the ingestion gave values in the diabetic range, although no family history of diabetes was reported. Another glucose tolerance test 2.5 months later gave values in the high normal range. During this test, the patient's urine contained a considerable amount of sugar.

Gitelson et al [29] stated that the cause of the persistent hyperglycemia in this patient was unknown, but, in referring to published case reports, they mentioned that this effect had also been seen in other patients with acetone poisoning. They speculated that the hyperglycemia might have resulted from an increase in acetoacetate caused by a metabolite of acetone.

In 1964, Linari et al [30] reported on a study of 19 employees who worked with METHYL ISOBUTYL KETONE for 20-30 minutes daily during an 8-hour shift. The ketone was mixed with other substances, including acetone [31],

and the workers centrifuged the resulting suspension. Analysis of the workplace air showed methyl isobutyl ketone at 500 ppm (2,050 mg/cu m) near the centrifuge while it was operating and at 80 ppm (328 mg/cu m) at the far sides of the room [30]. The authors noted that the concentration of methyl isobutyl ketone was either minimal or undetectable at the end of the centrifuging operation and that the workplace was naturally aerated and had forced ventilation. The workers were required to wear appropriate masks during the operation.

Weakness, loss of appetite, headache, burning in the eyes, stomach ache, nausea, vomiting, and sore throat were reported by more than half of the workers [30]. Insomnia, somnolence, heartburn, and intestinal pain were less frequent. Four workers had slightly enlarged livers, and six workers had a nonspecific form of colitis. Skin lesions, found in three workers, varied from erythema to small areas of peeling after an initial dry dermatitis. The results of the clinical chemistry tests were essentially normal, with only slight variation. Skin lesions disappeared after workers used protective gloves and creams, suggesting that contact with liquid ketone was largely responsible for the dermal effects.

Linari et al [30] concluded that methyl isobutyl ketone irritated the conjunctiva and respiratory tract and produced disturbances of the gastrointestinal tract and CNS. While this conclusion is probably correct (ie, it seems likely that methyl isobutyl ketone could produce the effects noted), the possible role of other contaminants, such as acetone, seems not to have been evaluated.

In a followup study, Armeli et al [31] reexamined 14 of the original 19 workers studied by Linari et al [30]. As in the first study, clinical

chemistry tests were performed and work histories were taken. The authors [31] noted that, in the 5 years since the first study, work practices had been greatly improved. In addition, all workers were required to wear air masks and gloves and to use barrier creams in operations where methyl isobutyl ketone was used. Analysis of the workplace air showed methyl isobutyl ketone at 100-105 ppm (410-431 mg/cu m) near the centrifuge and 50 ppm (205 mg/cu m) at the sides of the room. The authors noted that exposures lasted for 15-30 minutes daily.

Armeli and coworkers [31] reported that the results of clinical chemistry tests (red blood cell count, urine sedimentation, liver function, serum protein electrophoresis, glycemia, cholesterolemia, and lipid fractions) were essentially normal. The symptoms reported in the earlier study had nearly disappeared. Dermal lesions were also markedly reduced, but slight liver enlargement persisted in two workers. A few workers still reported CNS and gastrointestinal disturbances. The authors concluded that the improvements in work practices and engineering controls had reduced the symptoms of adverse effects. However, this study suggests that exposure to methyl isobutyl ketone at 50-105 ppm may produce harmful effects on workers.

In a written communication to the ACGIH TLV committee (GD Ware, June 1973), a copy of which was given to NIOSH during preparation of this document, it was reported that workers exposed to ISOPHORONE at 5-8 ppm complained of fatigue and malaise. After improvements in ventilation, isophorone concentrations were lowered to 1-4 ppm, and there were no further complaints.

(c) Effects on Skin

Dermal effects resulting from topical application of ACETONE were investigated by Lupulescu and Birmingham [32]. Small glass tubes containing about 1 ml of acetone were inverted on the right forearms of seven volunteers and held in place with tape for 90 minutes. Acetone was similarly applied to a second site that had been covered with a protective gel containing 50% water, 25% glycerin, 10-15% cellulose-methasol gum, and 2-3% unspecified preservative. Only the protective gel was applied to a third site on the same forearm. After 90 minutes, skin appearance was checked, and 4-mm skin samples were taken by punch biopsy from the treated areas of the forearm. The tissue samples were immediately fixed and prepared for light and electron microscopy. For scanning electron microscopy, similar biopsy experiments were performed using larger samples. Control specimens taken before exposure were similarly examined.

Gross examination of the skin showed only mild edema and hyperemia after contact with acetone [32]. No abnormal features were observed on skin protected with the gel. A reduction and desquamation of horny layers with intercellular edema were observed by light microscopy in the specimens exposed to acetone alone. Vacuoles surrounding the nuclei of the cells of the epidermis, particularly the stratum spinosum, were seen with the electron microscope. The scanning electron microscope showed that, after exposure to acetone, the cells of the stratum corneum were edematous, intercellular spaces were enlarged, and the desmosomes, which connect the cells, were broken apart. The usually organized pattern of the surface cells of the skin was not seen. Skin that had been protected with gel showed less severe effects under the scanning electron microscope.

The data from this study [32] show that dermal exposure to liquid acetone for 90 minutes can produce gross changes of the skin and ultrastructural damage to the upper layers of the contacted skin.

(d) Effects on the Nervous System

Smith and Mayers [33], in 1944, described working conditions and health effects in two factories where ACETONE and METHYL ETHYL KETONE were used as solvents in the waterproofing of raincoats. In one factory, workers applied vinylite resins dissolved in methyl ethyl ketone or acetone to the raincoats with brushes. They were probably exposed through skin contact and inhalation of vapor. Room air samples in this factory showed methyl ethyl ketone at 398-561 ppm (1,170-1,650 mg/cu m) and acetone at 330-495 ppm (782-1,170 mg/cu m). The sampling and analytical methods were not mentioned.

The authors [33] described two cases of possible ketone intoxication in this factory. One woman, 18 years old, developed gastric problems and watery eyes while at work. A few hours later, she was found unconscious and was taken to a hospital. Acetone was detected on her breath, her reflexes were hyperactive, and her face and limbs had occasional twitches. She had an elevated pulse (112 beats/minute), but her blood pressure was normal (128/70). Less than an hour after she was hospitalized, the woman had responded to nikethamide treatment, and a severe headache was the only effect still apparent. She was released from the hospital 2 days later.

The second worker was a 19-year-old woman who fainted at work [33]. She had a convulsion while unconscious but regained consciousness before she was taken to a hospital. She was confused at the time of admission and

suffered from a headache, but she had recovered enough to be released within an hour.

Because the women were exposed to acetone, methyl ethyl ketone, and vinylite resins, it is unclear whether the signs and symptoms were produced by exposure to only one of the compounds or were additive or synergistic effects from a combination of compounds. The effects, primarily in the CNS, may have been produced by both ketones since both cause CNS depression in animals according to a Public Health Service investigation [34].

In the second factory studied by Smith and Mayers [33], methyl ethyl ketone was used as a solvent for the resin with which the raincoats were made. Workers immersed their unprotected hands in the solvent, and they were also exposed by inhalation. Concentrations of methyl ethyl ketone in the workroom air ranged from 300 to 600 ppm (882-1,760 mg/cu m). Several workers had adverse health effects as a result of exposure. Some had dermatitis so severely that they could not work. Two men had dermatitis on the face that was attributed to exposure to methyl ethyl ketone in the air. Several workers experienced numbness in the fingers and arms, and one had a similar effect in the legs, which weakened when he tried to walk. Another worker stated that his shoulder felt as though it was made of dough and did not belong to him.

In 1971, Berg [35] reported a case of retrobulbar neuritis in an 18-year-old seaman who had been exposed to METHYL ETHYL KETONE while removing paint from an airplane hangar. Two other men who also were exposed had only mild respiratory symptoms and conjunctival irritation. The seaman noted a dull headache, mild vertigo, and diminished vision in both eyes. Two hours after exposure, he was alert, but his vision in both eyes was

"reduced to counting fingers." His vision, which had been 20/20 when he began military duty, was now 20/200. At this time, he had blurred vision, lightheadedness, and nausea. Although the conjunctivae were slightly congested, the results of an ophthalmoscopic examination were normal. Testing showed marked enlargement of the blind spots and superior arcuate-type defects in both eyes. The author noted that the man's clothing had an odor like that of acetone.

About 10 hours after exposure, the man's blood was analyzed for the first time, and unspecified amounts of methanol and formaldehyde were found [35]. Thirty-six hours after exposure, his vision had returned to 20/20 and his visual fields were normal. Daily analysis of blood serum showed no formaldehyde and steadily decreasing levels of methanol. Throughout his 6-day hospital stay, he noted a daily lessening of his dizziness and nausea.

Berg [35] postulated that the subject had optic nerve toxicity induced by methanol formed from the metabolism of methyl ethyl ketone. Berg did not rule out the possibility that methanol itself was the cause of the illness, although he pointed out that methanol toxicity produced a different clinical picture.

In 1975, Viader et al [36] investigated a case of peripheral neuropathy in a 55-year-old worker exposed to methyl ethyl ketone and other compounds. The worker was hospitalized in January 1974 for a loss of muscular strength in his hands, bilateral paresthesia of the fingers, and fatigue when he walked. He had a moderate weakness in all muscles of both hands, predominantly in the extensors of the fingers and the dorsal interosseal muscles, as well as weakness of the anterior tibial compartments of the legs. Tendon reflexes were present and normal, and

there was no amyotrophy or fasciculation. All signs of objective sensitivity were normal.

Viader et al [36] reported that an electromyogram showed peripheral neurogenic signs in all four limbs. Motor conduction velocities were slowed slightly in the external popliteal branch of the sciatic nerve. The man had no history of alcoholism, and his serum lead concentration (0.20 mg/liter) was normal. The authors noted that, 2.5 months after the worker was hospitalized, he had only a moderate weakness of the extensors of the fingers and the interossei of both hands and that his condition was judged to be further improved 10 months after the initial examination.

For 2 years before he was hospitalized, the worker had used a special adhesive and solvent to set plastic pipes into trenches about 2 meters deep [36]. Analysis of these products showed that the adhesive was 60% tetrahydrofuran and 40% polyester-type polymer. The solvent used to dissolve the adhesive was said to be 100% methyl ethyl ketone, but it is not clear if an analysis was performed. The author reported that the worker had manipulated the adhesive without gloves, cleaned his hands with the solvent, and inhaled the vapor at the bottom of the trench without a mask. Viader et al noted that the symptoms were similar to those of methyl n-butyl ketone poisoning (described in the study by Allen et al [37] discussed below). The authors concluded that the illness was caused by tetrahydrofuran, methyl ethyl ketone, or a combination of these agents. Although there is little doubt that this worker had signs of neurotoxicity, it is not clear what the causative agent was.

In August 1973, a case of severe peripheral neuropathy was diagnosed in a 22-year-old man who had worked for 2.5 years in the printing

department of a coated-fabric plant in Ohio, where some 275 chemicals, including METHYL ETHYL KETONE and METHYL n-BUTYL KETONE were used [37,38]. Since he was otherwise healthy, the symptoms were thought to be associated with exposure to a toxic chemical. The worker indicated that several others in the printing department had similar symptoms. An investigation was begun to identify neuropathy in other workers at the coated-fabric plant and to determine the causative agent. The investigation was conducted and supervised by a team of consultants from the company, the union, a hospital, the state health department, NIOSH, and the Center for Disease Control. The results of the investigation, discussed in detail in Epidemiologic Studies, implicated methyl n-butyl ketone as the probable cause of the neuropathy.

Allen et al [37] described the symptoms of the 22-year-old worker, which they considered to represent a typical case of motor and sensory neuropathy. He first noticed intermittent tingling sensations in his arms and legs, as if his limbs were "asleep"; those sensations progressed to weakness of the left leg about 3 months later. The leg weakness became worse, footdrop developed, and he had impairment of grip. The man lost 15 pounds over 8 months and was hospitalized after his condition was diagnosed as peripheral neuropathy. Physical examination showed prominent atrophy and occasional fasciculations of the intrinsic muscles of both hands. The man had severe weakness of the finger extensors and the dorsal and ventral interossei muscles and moderate weakness of the finger flexors and wrist pronators, supinators, extensors, and flexors. He also had moderate weakness of the iliopsoas, slight involvement of the quadriceps and hip adductors, bilateral footdrop, and severe weakness of the gastrocnemii, toe

extensors, and toe flexors. Except for absent finger jerks, reduced knee and hamstring reflexes on the right, and absent ankle jerks, the tendon reflexes were normal. Sensory testing showed a dense, bilateral loss of fast pricking pain over the toes, soles, and heels with a milder loss in the knees and similar defects in the hands up to the wrists. Temperature discrimination was impaired up to the knees, and light touch sensation was lost over the toes and fingers. Right peroneal nerve conduction velocity was slowed. Deep sensation was normal. Electromyography showed positive waves and fibrillations in many muscles. Other laboratory findings were essentially normal. Eight months after the man was hospitalized, his condition had markedly improved.

The authors [37] also described a case of motor neuropathy in a 43-year-old man who had been a pan washer at the coated-fabric plant for 18 years. He first noted a tendency of his knees to give way; this was followed by difficulty in picking up his feet, lifting heavy objects, and gripping small objects with his fingers. He reported a recent 25-pound weight loss. He was hospitalized and was found to have moderate, distal weakness of the arms and legs and mild, proximal weakness of the legs. Tendon reflexes and the results of sensory examinations were normal. An electromyogram showed positive waves and fibrillations in the distal muscles of the hands and a slowing of peroneal conduction velocities. Other laboratory findings were essentially normal. The man's condition was diagnosed as peripheral neuropathy of an undetermined origin. The condition of the man steadily improved, but he had slight weakness in the left ventral interossei. Otherwise, his strength was normal, and there was no atrophy.

Allen et al [37] next described a case of sensory neuropathy. A 55-year-old man, who had been a print operator for 27 years in the coated-fabric plant, first had a continuous sensation of his toes being "asleep," aching pain in the calf, and occasional momentary loss of balance or a feeling of lightheadedness. He also noted general fatigue, especially when carrying heavy loads. The man estimated that he had lost 50 pounds over the last 10 months. The results of a motor examination were entirely normal, showing completely normal strength and no atrophy or fasciculations in any muscle groups. All tendon reflexes were present and normal. Sensory examinations showed a decrease in temperature discrimination, in fast pricking pain, and in light touch over the entire right foot to the ankle and on the toes of the left foot. There was a similar sensory loss in all of the fingers of the right hand and in the fingertips of the left. Deep pain and position senses were normal. An electromyographic examination showed positive waves and fibrillations in extensor and flexor hallucis longus muscles. A followup examination, 7 months after the initial symptoms began, showed substantial improvements, but the man still had numbness of the toes and a loss of discrimination of superficial pain, temperature, and touch in both large toes. Electromyography showed only occasional positive waves without fibrillations in the left extensor hallucis longus.

In screening 1,157 employees by electrodiagnostic examinations, interviews, and a questionnaire, Allen et al [37] identified 194 suspected of having peripheral neuropathy or other neurologic disorders. These employees were examined by electromyography and laboratory studies and were later given followup examinations. Eighty-one were either normal or showed

results that were of doubtful importance to the study. Twenty-seven had neurologic disorders other than toxic polyneuropathy, such as diabetic neuropathy. Toxic polyneuropathy was diagnosed in 86 workers. Eleven of these had characteristic, disabling, peripheral neuropathy that was rated moderate to severe, and 38 had signs of neuropathy and characteristic electrodiagnostic abnormalities that were rated mild. Of the 86, 37 had no objective clinical findings, but they did have characteristic electrodiagnostic abnormalities and were classified as having minimal motor involvement.

The authors [37] described the neurologic pattern as a distal, motor, and sensory disorder that had an insidious onset with minimal loss of reflexes. Initial symptoms in those workers with prominent motor involvement included slowly developing weakness of the hands or feet accompanied by slapping gait or by difficulty moving their fingers or grasping heavy objects. Others had intermittent tingling paresthesia of the hands or feet. Pain was minimal or absent. Of the 10 patients in the group moderately to severely affected, in which body weight was monitored, 8 experienced weight losses ranging from 3-60 pounds. In the milder cases, no substantial weight changes were observed.

In the 11 moderate to severe cases, a combination of motor and sensory loss or of motor and reflex loss was observed [37]. In the 38 mild cases, sensory loss predominated. Muscle weakness commonly involved the intrinsic muscles of the hands and feet and the long extensors and flexors of the digits. Sensory loss was roughly symmetrical and was usually confined to the feet or fingers. Loss of reflexes was minimal, and no evidence of autonomic dysfunction was seen. Cranial nerve abnormalities

were noted in only one patient, who had unilateral sensory loss on the face. The authors noted that about one-sixth of the affected subjects continued to show progressive dysfunction for 3-5 months after all possibility of exposure had been eliminated.

Summarizing their electrodiagnostic findings in these workers, the authors [37] stated that electromyographic abnormalities were approximately symmetrical and were either restricted to a distal distribution or greater in degree in distal muscles than in proximal ones. In the moderately to severely affected group, positive waves and fibrillations were found in all 11 employees. Eight of these workers also had abnormal motor unit potentials. In the 38 mild cases, 31 had positive waves, 22 had fibrillations, and 23 had motor unit potential abnormalities. In the 37 cases of minimal involvement, 29 had positive waves, 16 had fibrillations, and 16 had abnormalities in motor unit potential. After serial examination, positive waves and fibrillations subsided, but polyphasic and abnormally large motor unit potentials became more abundant. The authors noted that, in general, electromyograms and nerve conduction velocities correlated with the clinical severity of neuropathy. The results of clinical chemistry tests were within normal ranges; however, significantly lower erythrocyte cholinesterase activities ($P<0.001$) and significantly higher plasma cholinesterase activities ($P<0.001$) as compared to volunteers and neurologically normal patients were found. Cholinesterase activities did not correlate with severity of the neuropathy. The significance of the lower erythrocyte cholinesterase activities and elevated plasma cholinesterase activities is not clear, though liver cell damage might explain the changes in plasma esterases.

To determine the causative agent, Allen et al [37] and Billmaier et al [38] investigated the processes and chemicals used in the plant and correlated this information with the incidence of polyneuropathy in various departments. These findings are reported in Epidemiologic Studies.

In 1976, Mallov [39] reported on spray painters who had worked with two formulations of paint on the Cannelton Dam and the Newburgh Dam. The older formulation contained 22% methyl isobutyl ketone and 22% methyl isoamyl ketone. In the new formulation, these two solvents were replaced by 44% methyl n-butyl ketone. Both formulations contained 3.1% of a tricresyl phosphate plasticizer. Gas-liquid chromatographic analysis by NIOSH did not detect triorthocresyl phosphate in the paint. The limit of sensitivity of this method was 0.1% by weight. The new formulation, containing methyl n-butyl ketone, was first used sometime after September 15, 1972, at Cannelton, where over 22,900 liters were used; at Newburgh, it was first used sometime after July 1972. Because there were no handwashing facilities, some workers washed their hands with paint thinners, including one containing methyl n-butyl ketone. Twenty-six men who worked at the two sites were examined, and medical and occupational histories were taken during the spring of 1974. Three men had clinical evidence of peripheral neuropathy.

One of the men with peripheral neuropathy was a 42-year-old painter who had worked on the Cannelton Dam from September 1972 until August 1973 [39]. In July 1973, he complained of weight loss, numbness and tingling in his feet, and a progressive weakness in both legs which progressed to his arms. His condition deteriorated so that he could not stand up without help or even turn a key in a lock. Examination showed bilateral footdrop

and an absence of ankle jerks, knee jerks, and brachioradialis reflexes. Sensation was mildly diminished or normal in the fingers and feet bilaterally. An electromyogram showed an increase in insertional activity, fibrillation potentials, positive sharp waves, and many polyphasic muscle potentials. The left median nerve latency was increased, while the conduction velocity was decreased. Alcoholism, diabetes, cancer, uremia, collagen diseases, and porphyria were ruled out as causative agents. Blood lead levels were mildy elevated (55 μg/100 ml), but a 24-hour urine sample contained normal lead levels (67 μg/liter). Normal and elevated levels were judged from statements taken from a chapter on metal poisoning in a medical text book [40]. An EDTA provocative test indicated a previous absorption of lead that was described as excessive. The worker had used lead paint extensively until 1.5 years before the onset of his illness. These blood and urine lead levels were probably not sufficiently high to have been associated with neuropathy, but a high body burden sufficient to have caused neuropathy may have existed.

The second case was that of a 35-year-old man who had been a painter at Cannelton from April to October 1973 [39]. His initial symptoms were tingling in his extremities, burning and freezing sensations in the soles of his feet, cramps in his calves, and weakness in his legs and hands. The worker eventually was unable to rise from a sitting position without help, and he could not push down the top of his shaving-cream can. Examination showed a bilateral footdrop and a left wristdrop. Muscle weakness was apparent in the distal muscles of the arms and legs and in the proximal muscles of the legs. Reflexes in both legs were said to be markedly diminished. His condition subsequently improved, but the absence of ankle

jerks and weakness in the foot persisted. Sensation was mildly impaired distal to the midcalf and midforearm. Two 24-hour urine specimens contained normal levels of lead (5.1 and 8 μg/liter). Nothing was found in the man's medical history to explain his condition.

The third case was that of a 43-year-old painter who had worked at the Cannelton Dam from September 1970 to April 1972 and from October 1972 to April 1973 [39]. He had also worked at the Newburgh Dam from April 1972 to October 1972 and from April 1973 to November 1, 1973. In October 1973, he noticed weakness in his feet, legs, and hands and numbness and tingling in his hands and feet. He noted in November that his feet were slapping down consistently when he walked, and he fell 25-30 times during the last few weeks of November and the 1st week of December. During this time, he had constant numbness in both feet and legs below the midcalf, and he experienced numbness in his hands and wrists for several hours two or three times each day from November 1 until the middle of December. He also had transient tingling on the backs of his hands, which was provoked by rubbing, and steady aches in his calves. When he was examined 3.5 months after the onset of his illness, he no longer had sensory symptoms but his lower extremities still felt weak. He also had an absent right ankle jerk, weakness in his right foot, and diminished pinprick, light touch, and vibratory sensation in his right foot. Blood lead levels were normal (25 μg/100 ml). Mallov [39] stated that all three workers, according to their work histories, had ample opportunity for respiratory and skin absorption of methyl n-butyl ketone and that all had developed neuropathy within 4 months of each other. The first patient had the greatest opportunity for skin absorption, since he did not wear gloves and changed his work clothes

only once a week. Mallov stated that, although the first patient had a previous exposure to lead, lead probably did not play a role in his neuropathy, because sensory loss is not characteristic of lead neuropathy. Mallov also believed that the tricresyl phosphate present in the paint had no relationship to the onset of neuropathy, since none of the ortho-isomer was present and since tricresyl phosphate had been used by the Army Corps of Engineers for 24 years without incident.

Davenport et al [41] have also described a case of progressive polyneuropathy in a 35-year-old furniture finisher. Unlike his coworkers, the man sometimes did not use his face mask and he often used a thinner to clean his hands. Six months before the man became ill, the manufacturer of the lacquers and solvents used in this process had substituted methyl n-butyl ketone for methyl isobutyl ketone on a volume for volume basis. Methyl n-butyl ketone was present in a concentration of 20% in the finish, 12% in the thinner, and 7% in the sealer. Toluene, xylene, n-butyl alcohol, and acetone were also present in various proportions, and the thinner contained 5% methanol.

The man first noticed tingling in his feet and mild clumsiness while walking. Two weeks later, he was unable to walk. He also developed paresthesia in his fingers. Three months later he was much stronger and was able to walk unassisted. A sural nerve biopsy taken at this time showed enlarged axons and axons packed with fine filaments measuring 10-15 nm in thickness, which were very similar to those described by Allen et al [37].

RL Barnes (written communication, January 1978) informed NIOSH of the occurrence of peripheral neuropathy in workers employed in a dewaxing unit

of a Texas refinery. The dewaxing unit uses a conventional solvent extraction method for removing high melting point hydrocarbons from petroleum to produce oils with adequate lubricating properties over a broad temperature range. This process involves mixing methyl ethyl ketone and toluene with various petroleum fractions. Airborne methyl ethyl ketone and toluene were found in the workroom.

NIOSH initiated a health hazard survey of this operation, but, until the investigation and data evaluation have been completed, no conclusions can be drawn at this time.

(e) Absorption and Excretion Studies

Cesaro and Pinerolo [24] studied the percutaneous absorption of ACETONE in volunteers. Eight healthy men with no evident physiologic disturbances were enclosed nude in a sealed box for 20-30 minutes with their heads protruding through a hole in the box. Cotton compresses were used in an attempt to saturate the chamber with acetone. Each subject breathed through a rubber mask with tubes leading to another room. Acetone was sprinkled on each subject's skin with a cotton compress during the exposure. Total ketone bodies in the blood, which included preformed acetone and acetone derived from diacetic acid or beta-oxybutyric acid, was determined before and immediately after exposure. The average value before exposure was 0.89 mg%, while after exposure it was 0.90 mg%. They concluded that acetone was not absorbed through healthy human skin.

Using the apparatus of Cesaro and Pinerolo [24], Parmeggiani and Sassi [27] studied the percutaneous absorption of acetone. The method was the same except the subject lightly applied acetone to his skin with a saturated cotton pad for 30 minutes. A total of 15 g of acetone was used.

The subject was then kept in the chamber for 1.5 hours. After the exposure, blood acetone levels were 40 mg/liter as compared with only a trace before exposure. Acetone concentrations in the urine were 10 mg/liter before exposure and 70 mg/liter at the end of exposure. These data indicate that acetone was absorbed through the skin. The apparent contradiction between these results and those obtained by Cesaro and Pinerolo are most likely attributed to the longer period of exposure. Also, there was a greater chance in this study for liquid acetone to contact the skin. From these studies, it appears that percutaneous absorption of acetone is dependent on the extent of exposure.

DiVincenzo et al [42], in 1973, reported acetone excretion and blood chemistry changes in humans exposed to acetone vapor. Nine male employees, aged 22-62 years, volunteered to participate in the experiment, but participation was contingent on medical approval. It is unclear whether all nine participated in the experiments. Those that did participate fasted for 8 hours before they were exposed to acetone at 100 or 500 ppm (237 or 1,185 mg/cu m), followed by 2 hours at rest, 2 hours with exercise, or 4 hours at rest. They avoided using toothpaste and mouthwash because they might contain contaminants that could interfere with the analysis. Those who exercised either remained seated or jogged for 5 minutes and rested for 10 minutes. Before exposure and 24 hours later, blood samples were collected for hematologic and clinical chemistry testing. Exhaled breath, venous blood, and urine samples were also collected at regular intervals during and after exposure. These samples were analyzed for acetone by gas-liquid chromatography. The authors [42] concluded that there was no appreciable change in the blood chemistry of any of the

subjects exposed to acetone at 100 or 500 ppm for 2 or 4 hours. However, for those exposed for 4 hours, no clinical data (blood chemistry) were reported. It is unclear, in addition, whether or not the clinical data presented were those for men who exercised; since the authors reported a twofold increase in acetone absorption during exercise, which was not reflected in an increase in the urine acetone concentration, the clinical data for men who exercised might have differed from those who did not exercise.

Analysis of the subjects' expired air during the 2-hour exposures and up to 7 hours afterwards showed that, after the first 15 minutes, approximately 75-80% of the inspired vapor was absorbed by the blood and 20-25% remained in the dead space volume [42]. The ratio of acetone absorbed to that eliminated remained constant during exposure, indicating that body compartment saturation did not occur. The exposure concentration of acetone and the concentration in the expired air were directly proportional both during and after exposures. The wash-out curves of the vapor showed that, up to 7 hours after exposure ended, acetone was not entirely eliminated from the body. However, data on the normal concentration of acetone in expired air were not given. The character of these curves suggested to the authors that repeated daily exposures at higher concentrations would allow acetone to accumulate in the body.

The concentrations of acetone vapor in the breath also depended on length of exposure and intensity of exercise during exposure at 100 ppm for 2 hours [42]. Increasing the exposure from 2 to 4 hours caused an increase in postexposure respiratory excretion of acetone, but the excretion was less than twice that measured for the 2-hour exposure. The significance of

these findings is uncertain because of the small number of subjects used in the study and the wide variation in concentrations. Assuming the uptake to be directly dependent on time and concentration, this decrement indicated that excretion was carried out through other routes, such as urinary or percutaneous, or that metabolic breakdown of the acetone was occurring. The increased excretion in the exercising subjects indicated that the increase in minute volume resulting from the exposure was responsible for an increased uptake of the acetone vapor.

Analysis of whole blood samples for acetone showed that a 2-hour exposure was not sufficient to produce steady-state conditions [42]. This exposure duration was too short to allow saturation of the body water compartment. The half-life of the acetone in the blood was calculated to be about 3 hours for subjects at rest who were exposed at 100 ppm for 2 hours, and the authors concluded that their postexposure results indicated that acetone disappeared from the blood at a constant rate that was independent of the initial concentration (zero-order kinetics).

Analysis of urine for acetone did not show a relationship that was directly proportional to the exposure concentration [42]. However, no attempt was made to regulate urinary volume during the collection period, so this relationship might be directly proportional under rigorously controlled conditions.

DiVincenzo et al [42] concluded that the absorption of acetone by humans was directly proportional to the magnitude of exposure. They also pointed out that physical activity increased absorption and that absorption was related to the minute volume of air breathed. They suggested that, since the concentrations of acetone in expired air and blood were directly

proportional to the extent of exposure, these indices might be used for biologic monitoring. The authors' finding that acetone can accumulate in the body is significant because it suggests that longer periods of exposure may produce toxicity.

Munies and Wurster [43] investigated the percutaneous absorption of METHYL ETHYL KETONE in volunteers. Absorption was studied using hydrous, anhydrous, and normal skin. An absorption cell that was previously described by Wurster and Kramer [44] was used to keep the ketone in contact with the forearm of the subject. For hydrous conditions, water was mixed with methyl ethyl ketone in the cell. For anhydrous conditions, the cell was first filled with magnesium perchlorate. Expired air was analyzed by gas chromatography. Exposures lasted 8 hours.

The authors [43] reported that methyl ethyl ketone was found in the expired air 2.5-3 minutes after contacting normal skin. A plot of the concentration of the ketone in expired air showed that a plateau value for elimination was reached in 2-3 hours. In anhydrous skin, the plateau value was reached in 4-5 hours. Under hydrated skin conditions, methyl ethyl ketone was found in the expired air within 30 seconds; the concentration rose to a maximum in a few minutes and then declined to a plateau in about 2 hours.

The authors [43] supplied data on the analysis of one sample of expired air which showed chromatographic peaks corresponding to those for methyl ethyl ketone, acetone, acetaldehyde, methanol, and ethanol. Munies and Wurster did not discuss these results, but the data may indicate that these compounds represent biotransformation products of the methyl ethyl ketone used in this study. However, the data might also represent

contamination of the methyl ethyl ketone used in this study inasmuch as the authors did not present any information on the source or purity of their sample. This investigation demonstrated that methyl ethyl ketone is rapidly absorbed through the skin and is rapidly excreted in the expired air.

In 1978, DiVincenzo et al [45] reported on the respiratory uptake, excretion, and skin absorption of METHYL n-BUTYL KETONE in humans. Three men, aged 22-53 years, were exposed to air containing methyl n-butyl ketone at 100 ppm (410 mg/cu m) for 4 hours and at 10 or 50 ppm (41 or 205 mg/cu m) for 7.5 hours with a half-hour lunch break after 4 hours of exposure. For skin exposures, the absorption cell method of Munies and Wurster [43] was used to determine the absorption of liquid 14C-methyl n-butyl ketone and the influence of methyl ethyl ketone on the absorption of methyl n-butyl ketone in a 9:1 mixture (by volume). Fifteen milliliters of methyl n-butyl ketone or the ketone mixture, each containing 20 microcuries of 1-14C-methyl n-butyl ketone, was placed in contact with a shaved area on the inner forearm for 60 minutes. Precautions were taken to ensure that the ketones were not inhaled. Skin absorption was calculated from the 12-hour cumulative excretion of radiolabeled methyl n-butyl ketone in breath and urine. Two volunteers also ingested 2 microcuries of 1-14C-methyl n-butyl ketone in a dose of 0.1 mg/kg. The 12-hour cumulative excretion of radioactivity in breath and urine was compared with the 12-hour excretion from volunteers exposed by skin contact.

In humans exposed to methyl n-butyl ketone at 10 and 50 ppm for 7.5 hours, the mean breath concentration was 1.4 and 9.3 ppm (5.7 and 38.1 mg/cu m), respectively [45]. Fifteen minutes after exposure at 10 and 50

ppm, the expired air contained 0.1 and 0.5 ppm (0.4 and 2.0 mg/cu m), respectively, and, 3 hours after exposure at 50 and 100 ppm, no methyl n-butyl ketone was found in the expired air. Exposure to methyl n-butyl ketone at 100 ppm for 4 hours produced an average breath concentration of 22 ppm after 2 hours of exposure. The authors noted that between 75 and 92% of the vapor inhaled was absorbed, with greater retention at lower concentrations.

During and after exposure at 10 or 50 ppm, no methyl n-butyl ketone was found in the serum; however, it was detectable during exposure at 100 ppm [45]. Neither methyl n-butyl ketone nor its metabolites were detected in the urine during or after exposure. However, 2,5-hexanedione was found in the urine for 1-3 hours after exposure.

Two volunteers, given methyl n-butyl ketone orally, excreted a maximum amount of 14C-labeled carbon dioxide at 4 hours after exposure. Eight days after the subjects received methyl n-butyl ketone, 39.5% of the dose had been excreted in the breath, while 26.3% of the dose had been recovered in the urine.

Methyl n-butyl ketone was readily absorbed through the skin, both alone and in combination with methyl ethyl ketone. When only methyl n-butyl ketone was applied, two volunteers absorbed 16.0 and 26.8 mg, respectively, about 0.1% or more of the amount applied; when the mixture was applied, the amount of total solvent absorbed was reported as 14.0 and 18.7 mg. The authors reported that the absorption rates ranged from 4.2 to 8.0 μg/minute/sq cm for pure methyl n-butyl ketone and the mixture with methyl ethyl ketone. However, it is not certain that the total solvent absorbed from the mixture contained methyl ethyl ketone and methyl n-butyl

ketone in a 9:1 ratio, since radiolabeled methyl ethyl ketone was not used.

The authors [45] concluded that methyl n-butyl ketone was readily absorbed through the lungs, gastrointestinal tract, and the skin and that it was metabolized by at least two pathways, one forming respired carbon dioxide and the other forming 2,5-hexanedione. The major metabolite was respiratory carbon dioxide.

DiVincenzo and colleagues [45] pointed out that the absorption of methyl n-butyl ketone through human skin can be substantial. Assuming that the surface area of the hands is about 0.074 sq m and that the rate of absorption of methyl n-butyl ketone was 5 μg/minute/sq cm, they calculated that 222 mg would be absorbed through the skin in 1 hour. By comparison, exposure to methyl n-butyl ketone at 25 ppm for 1 hour by inhalation would result in absorption of 92 mg, assuming a minute volume of 20 liters/minute and 75% absorption by the lungs. This study, then, demonstrates that percutaneous absorption can be an important route of exposure to methyl n-butyl ketone.

Epidemiologic Studies

In 1973, NIOSH was involved in an intensive and concerted occupational health investigation involving several state, Federal, and private organizations [46]. The purpose of this investigation was to determine the causative agent in an outbreak of peripheral neuropathy in workers employed in a coated-fabric plant. Allen et al [37] and Billmaier et al [38] reported their findings on this outbreak. Clinical findings from these workers and three typical cases of peripheral neuropathy, as reported by Allen et al [37], have been described in Effects on Humans.

Billmaier et al [38] also presented data on the same population, although they reported slightly different figures.

Additional cases of suspected neuropathy were initially identified in print department workers through clinical examination and a short neurologic history [38]. Workers suspected of having neuropathy received electrodiagnostic tests, including electromyogram and nerve conduction studies. Because these tests are objective and sensitive, the investigators then decided to use electromyograms and nerve conduction tests to screen all workers at the plant for evidence of subclinical peripheral neuropathy after slight abnormalities were found in the tests of selected workers not employed in the print department.

The electromyograms and nerve conduction tests of 192 of the 1,157 workers examined (17%) had abnormalities that could be associated with peripheral neuropathy [38]. After the employees received clinical evaluations, the investigators classified findings on these 192 workers by using a rating scale based on signs, symptoms, and electrodiagnostic tests. They reported that findings from 72 workers were within normal limits, 24 were not indicative of any definite abnormality, 28 were indicative of suspected abnormality, and 68 were indicative of peripheral neuropathy.

Using data from questionnaires or from company records, Billmaier et al [38] determined that, of those workers with definite evidence of peripheral neuropathy, 21.9% were from the print shop (38 of 173) and only 3.0% were from other departments (30 of 984). The difference between the percentages is statistically significant ($P<0.001$, using a chi-square test). Twenty of the 68 workers had diabetes or other conditions that can cause or contribute to neuropathy; 2 worked in the printing department and

18 worked in nonprinting departments. None of the workers in the nonprinting departments had severe peripheral neuropathy. Of the 38 workers from the print department with peripheral neuropathy, 27 operated the printing machines, 10 were helpers, and 1 washed ink pans by hand with recovered solvent. Nine of these workers had severe peripheral neuropathy. Operators spent virtually all of their time, and the helpers spent about half their time, near the printing machines when they were running. The number of print-department workers developing neuropathy, by job category, is compared with data from other departments in Table III-2.

Neuropathy was more prevalent in those who ate on the job and in those who worked overtime [38]. Printing department workers who developed peripheral neuropathy ranged from 20 to 57 years of age and had worked in the area for 5 weeks to 27 years. However, printing department workers who developed peripheral neuropathies did not differ significantly in either age or length of employment from those who did not develop the condition ($P>0.05$). Workers with peripheral neuropathy from other departments tended to be older than affected workers from the printing department ($P<0.05$) and older than workers in the other departments who did not develop neuropathy ($P<0.05$).

Symptoms were first noticed by 89% of the workers (34 of 38) between December 1972 and September 1973 [38]. These symptoms started most frequently in the summer months. In contrast, only 53% of the workers (16 of 30) in the other departments first noticed symptoms of neuropathy between December 1972 and September 1973, and the onset of symptoms was distributed more evenly throughout the 10 months. The condition of all

TABLE III-2

OCCURRENCE OF NEUROPATHY IN EMPLOYEES EXPOSED TO METHYL n-BUTYL KETONE IN PRINT AND NONPRINT DEPARTMENTS

Group	Ill	Not Ill	Total
Nonprint departments	30*	954	984
Print department (total)	38**	135	173
Operators***	27	42	69
Helpers***	10	49	59
Foremen	-	21	21
Service helpers	1	15	16
Not known	-	8	8
Total, all departments	68	1,089	1,157

*Includes 18 persons with diabetes or other conditions that can cause or contribute to neuropathy
**Includes 1 person with diabetes and another on isoniazid therapy
***Operators required to be close to the printing modules virtually 100% of their time had a significantly higher incidence of peripheral neuropathy ($P<0.001$) than helpers who spent about 50% of their time at the printing machines.

Adapted from reference 38

employees with peripheral neuropathy who worked in the print department improved after they were removed from exposure.

The investigators [38] tentatively concluded that the incidence of peripheral neuropathy in workers from other departments represented a

background level in a working population. They cautioned, however, that these workers were not a true control group, since the condition of workers in other departments with peripheral neuropathies improved when they were away from work.

To identify the agents most likely associated with the development of neuropathy, the investigators [38] obtained information on work practices and production, including any changes that might have occurred. The inks used in the printing department contained resins, stabilizers, plasticizers, pigments, and solvents, but the investigators noted that mists were not formed from the inks. This statement was apparently based on visual observation. They concluded that the workers were exposed primarily to solvents by skin contact and to solvent vapors by inhalation. The investigation revealed that apparently there had been no recent increase in the concentration of any of the airborne compounds used in the printing process. The substitution of methyl n-butyl ketone for methyl isobutyl ketone was the only major process change that had occurred in the past 7 years. To comply with community air pollution requirements, plants in other states owned by the same company had begun to substitute methyl n-butyl ketone for methyl isobutyl ketone. (According to the authors, methyl isobutyl ketone is photochemically reactive and thus can be a factor in the formation of smog.) At this plant, substitution of methyl n-butyl ketone for methyl isobutyl ketone began in August 1972 and was completed in January 1973.

Five or 10-minute area samples were taken near 9 of the 17 printing machines and analyzed by gas chromatography for 9 solvents (methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, hexane, toluene,

xylene, methyl alcohol, acetone, and mineral spirits) and for methyl methacrylate [38]. Average concentrations of airborne methyl ethyl ketone were 331 ppm (976 mg/cu m) in front of the printers (range 104-670 ppm; 307-1,976 mg/cu m), 516 ppm (1,522 mg/cu m) in back of the printers (range 85-763 ppm; 251-2,250 mg/cu m), and 147 ppm (434 mg/cu m) in the nearby "wind-up" area (range, 39-338 ppm; 115-997 mg/cu m). The average air concentrations of methyl n-butyl ketone were 9.2 ppm (37.7 mg/cu m) in front of the printers (range 2.3-21.7 ppm; 9.4-89.0 mg/cu m), 36.0 (147.6 mg/cu m) ppm in back of the printers (range 2.5-156.0 ppm; 10.2-639.6 mg/cu m), and 6.1 ppm (25.2 mg/cu m) in the wind-up area (range 1.0-17.5 ppm;4.1-71.8 mg/cu m). The concentrations of the other eight airborne compounds were stated by the authors to be very low [38]. The investigators also found that the workers had not worn respirators or gloves, had eaten in the work areas, had washed their hands with solvent, and had used rags soaked with solvent to clean equipment and machinery.

Another report [47] indicated that no cases of neuropathy were found at a similar plant that used methyl ethyl ketone but not methyl n-butyl ketone. The results of electrodiagnostic studies of 21 workers in that plant were essentially normal. However, tetrahydrofuran was also used on occasion at the plant where cases of neuropathy developed. It was not used at the other plant.

Billmaier et al [38] and Allen et al [37] concluded that the outbreak of peripheral neuropathy in printing department workers was probably associated with exposure to methyl n-butyl ketone. Most of the printing department workers with peripheral neuropathy first noticed symptoms during the summer of 1973, about 6 months after the substitution of methyl n-butyl

ketone for methyl isobutyl ketone was completed. Production had been very limited, but no new cases of peripheral neuropathy were identified after methyl n-butyl ketone had been removed from the printing process. The authors stressed that exposures to airborne methyl n-butyl ketone near the printer were substantially below those recommended in the Threshold Limit Value (TLV) list.

Animal Toxicity

(a) General Effects

(1) Acetone

Studies conducted in the 1920's [48,49] indicated that single injections of acetone in a variety of experimental animals produced depression of the respiratory and vasomotor centers. In 1920, Sollmann [50] demonstrated that, when rats consumed 1.8 ml/kg of acetone/day, growth and food consumption were reduced. No rats died after 4 months of exposure. In 1927, Walton et al [51] compared the toxicities of diacetone alcohol and acetone. Diacetone alcohol was considered to be a polymer of acetone by the authors. Rats were injected iv with various amounts of the ketones. The authors concluded that diacetone alcohol was somewhat more toxic than acetone because narcosis developed more rapidly and there was a more constant depression of respiration. Both substances also decreased blood pressure.

DiVincenzo et al [42] exposed three male beagle dogs to acetone vapor at concentrations of 100, 500, and 1,000 ppm (237, 1,185, and 2,370 mg/cu m) for 2 hours [42]. A comparison of data from breath and blood samples from the dogs with the human data presented earlier showed that the dogs

absorbed about five times more acetone than did humans on a weight-corrected basis, but the breath concentrations were significantly higher in humans at similar intervals in the study. The postexposure blood acetone concentrations of the dogs were similar to those of humans, and the calculated half-life was also about 3 hours.

(2) Methyl Ethyl Ketone

In 1935, Patty and associates [19] described the effects of exposure to methyl ethyl ketone on guinea pigs. According to the manufacturer, the methyl ethyl ketone was 92.3% ketone as determined by acetylation. Information on impurities was not given.

Guinea pigs in groups of six were exposed to airborne methyl ethyl ketone at concentrations of approximately 10.0, 3.3, 1.0, and 0.33% by volume, as determined by an iodometric method, for various durations up to 810 minutes [19]. Twenty-four guinea pigs served as controls. The organs of animals that died during exposure and of some animals killed on the 4th and 8th days after exposure were examined macroscopically.

The authors [19] reported that the signs of toxicity exhibited by the animals were, in the order of occurrence, irritation of the nose and eyes, tearing, incoordination, narcosis, gasping, and death. The guinea pigs exposed to methyl ethyl ketone at 0.33% showed no abnormal signs during or after 810 minutes of exposure. Those exposed at approximately 1.0% showed irritation of the nose in 2 minutes and eyes in 4 minutes, tearing in 40 minutes, incoordination in 90 minutes, and unconsciousness in 240-280 minutes, but no gasping respiration or deaths occurred during or after 810 minutes of exposure. At the two higher concentrations of methyl ethyl ketone, the exposure time before these signs of toxicity appeared was much

shorter, and deaths occurred in 200-260 minutes at 3.3% and in 45-55 minutes at 10%. The authors did not specify the number of animals that died after each exposure.

The guinea pigs that died during exposure had emphysema, slight congestion in the brain, and marked congestion of the systemic organs, especially in the lungs [19]. All guinea pigs exposed at 10.0% for more than 30 minutes developed corneal opacities. These diminished, and they had nearly disappeared in most animals 8 days after exposure. The guinea pigs killed immediately after exposure of up to 180 minutes to methyl ethyl ketone at 3.3 and 10% had slight congestion in the brain and moderate congestion of the lungs, liver, and kidneys. These findings were absent in nearly all animals killed for necropsy 4-8 days after exposure. Whether this suggests reversibility of the morbid changes or differential susceptibility of test animals, eg, early deaths among animals with preexisting changes, is not clear.

These results show that methyl ethyl ketone at a concentration of 5-10% was dangerous to the life of guinea pigs in 30-60 minutes and that 0.3% was the maximum concentration that could be tolerated for several hours without serious disturbance [19]. It was not clear whether death was caused by irritation of the lungs or by narcosis. Methyl ethyl ketone has warning properties (eye and nose irritation) in concentrations that were apparently otherwise harmless to guinea pigs exposed for several hours.

(3) Methyl n-Propyl Ketone

In 1936, Yant et al [52] reported the effects of methyl n-propyl ketone on guinea pigs. Groups of six guinea pigs of unspecified sex and weight were exposed to methyl n-propyl ketone at concentrations of

1,500, 5,000, 13,000, and 50,000 ppm (5,250, 17,600, 45,760 and 176,000 mg/cu m) as determined by an iodometric method for up to 810 minutes. Twenty-four guinea pigs served as controls. The organs of some guinea pigs were examined macroscopically. Since the saturation concentration of the compound at 25 C is 21,000 ppm (73,920 mg/cu m), some of the compounds may have been present in particulate form at the higher exposures, even though they were apparently produced at 30 C.

The guinea pigs exposed at 1,500 ppm had no abnormal signs during the 810-minute exposure [52]. At 5,000 ppm, nose and eye irritation occurred in 3 minutes, tearing in 5 minutes, incoordination in 270 minutes, unconsciousness in 460-710 minutes, and labored breathing in 570-710 minutes, but no guinea pigs died during or after the exposure. The authors noted that the time of onset for these signs decreased rapidly with increases in concentration and that death occurred after 50 minutes of exposure at 50,000 ppm. The authors did not mention the number of animals in each group with these signs, but they did report that animals that did not die during exposure survived the 4- or 8-day observation period after exposure.

Animals that died during the exposure had slight congestion of the brain and marked congestion of the systemic organs, including lungs that were emphysematous, edematous, and markedly congested [52]. Animals with marked incoordination, narcosis, and a gasping-type respiration that were killed immediately after exposure had little or no congestion of the brain and slight to moderate congestion of the lungs, liver, and kidneys. These findings were absent in nearly all animals killed for necropsy 4-8 days after exposure. No gross abnormalities were found in animals exposed to

methyl n-propyl ketone for 270 minutes at 5,000 ppm and for up to 810 minutes at 1,500 ppm.

These results [52] show that exposure to methyl n-propyl ketone at a concentration of 50,000 ppm for 30-60 minutes was lethal to guinea pigs. The authors' findings show that methyl n-propyl ketone caused death by narcosis and that the principal gross abnormalities were congestion, edema, and hemorrhage of the lungs, liver, and kidneys of the guinea pigs. The authors noted that a concentration of 1,500 ppm of methyl n-propyl ketone could be tolerated by guinea pigs for several hours with only slight signs or no signs at all.

(4) Methyl Isobutyl Ketone

MacEwen et al [53] exposed rats, mice, dogs, and monkeys for 24 hours/day to methyl isobutyl ketone at concentrations of 100 or 200 ppm (410 or 820 mg/cu m) for 2 weeks and, in an experiment designed to evaluate toxicity under spacecraft cabin conditions, exposed dogs, rats, and monkeys to methyl isobutyl ketone at approximately 100 ppm for 90 days. The 2-week preliminary range-finding experiments were conducted in an altitude chamber at normal atmospheric pressure with an airflow of 40 cu ft/minute and a temperature of 22 C. Gas-liquid chromatography was used to determine the concentrations every 5 minutes from samples collected near the breathing zone of dogs. Four monkeys, 8 dogs, 40 mice, and 50 rats were exposed to methyl isobutyl ketone at each concentration and 3 monkeys, 4 dogs, 20 mice, and 25 rats, used as controls in identical inhalation chambers, received no ketone exposure. One monkey in each group was implanted with cortical electrodes for evaluation of CNS effects. Body weights and the results of clinical chemistry, hematologic, and electroencephalographic

(EEG) tests were determined before and after exposure. Organ-to-body weight ratios, macroscopic and microscopic tissue examinations, and blood pH and gas tests were performed. Spontaneous activity measurements were taken, and adverse signs were noted during the exposure.

The only findings in which exposed animals differed significantly from controls were heavier kidneys and higher kidney-to-body weight ratios in the rats exposed at 100 ppm and the higher liver and kidney weights and correspondingly increased organ-to-body weight ratios in rats exposed at 200 ppm [53]. Microscopic examination of the kidneys of exposed rats showed toxic nephrosis of the proximal tubules at both 100 and 200 ppm. The authors concluded that the kidney was the primary organ affected by methyl isobutyl ketone.

MacEwen et al [53] then conducted a 90-day exposure experiment. Two male Rhesus monkeys, 8 male beagle dogs, and 100 male Wistar rats were exposed for 24 hours/day at 5 psia (about one-third of an atmosphere) to methyl isobutyl ketone at about 100 ppm (410 mg/cu m). Controls consisted of an identical number of unexposed male animals. Every other week, starting 1 month before the exposure began, the dogs and monkeys were weighed and blood samples were taken for various hematologic and clinical chemistry determinations. Liver function tests were performed before and immediately after exposure, and serum acid phosphatase and serum glucuronidase determinations were made before exposure began and on the 30th and 60th days of exposure. After the 90-day exposure, two dogs were observed for 60 days to determine if the effects were reversible. The other dogs were killed and examined grossly, and organ samples were examined microscopically. Rats were weighed before exposure and every

other week during the exposure. Two exposed rats and two control rats were killed at weekly intervals for 3 weeks and then every other week thereafter, and their organs were grossly examined. After the rats had been exposed for 2 weeks, 10 were removed from exposure, and 2 of them were killed every 2 weeks and examined to determine if the kidney lesions seen in the short-term studies were reversible. At the end of the 90-day study, 10 rats were saved and were later killed serially for reversibility studies, 10 were killed for microscopic examination of tissues, and the remaining rats were killed and organ weights were determined.

The results of clinical chemistry and hematologic measurements in dogs and monkeys showed no significant differences between experimental and control animals [53]. Serum glucuronidase activity was much higher in exposed monkeys than in controls, but this condition also existed in baseline measurements. The authors did not relate this condition to methyl isobutyl ketone exposure. No differences between exposed and control dogs were found in sections of heart, lungs, brain, liver, spleen, kidneys, adrenal gland, or pituitary gland tissues. The only microscopic change found in monkeys was focal chronic inflammation of the kidneys in one exposed animal.

There was no statistically significant difference in the weight gained by exposed and control rats [53]. As in the 2-week exposure, the exposed rats had significantly heavier livers and kidneys ($P<0.01$) and corresponding increases in organ-to-body weight ratios for these two organs. All exposed rats showed hyaline droplet degeneration of the proximal tubules of the kidneys with occasional foci of tubular necrosis after the 90-day exposure. Rats removed from exposure after as few as 15

days also showed some kidney changes, although hyaline droplets grew larger with time. No adverse changes were observed in rat livers. Kidney tubular damage was reversible in those rats observed for 60 days after being exposed to methyl isobutyl ketone for 15 days. The rats exposed for 90 days recovered but did so more slowly than those exposed for less time.

(5) Diisobutyl Ketone

In 1953, Carpenter et al [20] studied the effects of single and repeated exposures to diisobutyl ketone on rats and guinea pigs. For single exposures, groups of six Sherman rats were exposed to diisobutyl ketone at a concentration of 2,000 ppm (11,640 mg/cu m). Seven of 12 female rats died after a single 8-hour exposure to diisobutyl ketone at 2,000 ppm, but all 6 exposed males survived [20]. The experiment was repeated with Carworth Farms Wistar rats using an undescribed number of males and females. All survived a single 8-hour exposure to diisobutyl ketone at 2,000 ppm. The authors concluded that the effects noted were due to differences in susceptibility between strains of rats.

In repeated exposure studies, groups of 15 male Sherman rats weighing 145-197 g and 15 females weighing 128-162 g were exposed for 7 hours/day, 5 days/week, for 6 weeks to diisobutyl ketone at concentrations of 125, 250, 530, 920, and 1,650 ppm (728, 1,455, 3,085, 5,354, and 9,603 mg/cu m), measured 4 times/day with an interferometer. In addition, groups of 10 male guinea pigs weighing 288-360 g were exposed at 125 or 250 ppm. Exposed animals and unexposed controls were weighed weekly, and the liver and kidneys were weighed at the termination of the study. The lungs, liver, kidneys, spleen, and adrenals of animals exposed to diisobutyl ketone at 250, 530, 920, and 1,650 ppm were examined microscopically,

except that only lungs, liver, and kidneys in animals exposed at 125 ppm were examined.

Exposure to diisobutyl ketone at 1,650 ppm killed all 15 female rats during the 1st day of exposure [20]. Only 2 of 15 male rats died, but all the males were prostrate at the end of the 1st day, and about half had poor coordination at the end of the 2nd day. These signs were not observed during the other 28 days of exposure. The 13 males that survived the 30-day exposure had reportedly significantly lower body weights and higher kidney and liver weights than did the controls (no P value given). No major microscopic changes were noted in the adrenals, kidneys, liver, lungs, and spleen of survivors, but five male rats had cloudy swelling of the liver, and eight had moderate lung congestion. The authors noted that 5 of 15 control males had similar lung involvement. Major lung, kidney, and liver abnormalities were found in the male and female rats that died during the 1st day of exposure.

No rats died when they were exposed for 30 days to diisobutyl ketone at 125, 250, 530, or 920 ppm [20]. Liver and kidney weights were significantly increased in male and female rats exposed to diisobutyl ketone at 920 and 530 ppm (no P value given). Similar organ weight increases occurred in females exposed at 250 ppm. There were no abnormalities noted in rats exposed at 125 ppm. Male guinea pigs had significantly lower liver weights after exposure to diisobutyl ketone at 250 ppm, but no P value was given [20]. No toxic effect in rats or guinea pigs was noted at 125 ppm.

(6) Cyclohexanone

In 1943, Treon et al [54] reported on the effects of cyclohexanone exposure on rabbits and monkeys. Groups of four rabbits of unspecified sex, age, and weight were exposed to cyclohexanone at average concentrations of 190-1,414 ppm (762-5,670 mg/cu m) for 6 hours/day, 5 days/week, for 10 weeks, and at 3,082 ppm (12,359 mg/cu m) for 6 hours/day, 5 days/week, for 3 weeks. In addition, one rhesus monkey was exposed at an average concentration of 608 ppm for 6 hours/day, 5 days/week, for 10 weeks. Cyclohexanone concentrations were determined colorimetrically throughout the exposures. Animal weights were determined daily, and microscopic examinations were performed 2 months after the termination of exposure.

Only the rabbits exposed at 3,082 ppm lost weight [54]. The body temperatures in exposed animals were similar to those of control animals, except in animals exposed at 3,082 ppm. In this case, the mean daily decrease was more than five times that observed in controls. Two of the four rabbits died at 3,082 ppm. They had no convulsions or tremors, but narcosis and incoordination were observed. Rabbits exposed at 3,082 ppm and at 1,414 ppm had distended ear veins, excess salivation, and conjunctival irritation throughout the daily exposures. Although narcosis and incoordination were not seen at 1,414 ppm, there was some lethargy. Exposures at 309 and 773 ppm (1,239 and 3,100 mg/cu m) produced less ocular irritation than did the exposures at higher concentrations. Exposure at 190 ppm produced no noticeable behavioral abnormalities. Cyclohexanone at 190 ppm induced barely demonstrable degenerative changes in the liver and kidneys of rabbits exposed for 300 hours. The authors reported that the

monkey exposed at 608 ppm for 300 hours had extensive injury to the heart muscle, lungs, liver, and kidneys.

The work of Treon et al [54], although it lacks experimental detail, does provide evidence that repeated exposure of rabbits to cyclohexanone at 190 ppm produces slight liver and kidney damage. The effects in the one monkey may not be appropriately attributed to the exposure, because it was suffering from a chronic bronchopulmonary infection.

(7) Mesityl Oxide

Hart et al [55] exposed mice and rabbits to saturated atmospheres of mesityl oxide. Concentrations were varied by changing the atmospheric temperature. Mice were exposed at concentrations ranging from 0.6 to 2.4%. Toxic signs included eye and nose irritation, gasping respiration, rocking convulsions, narcosis, vasodilatation, cyanosis, and death. Deaths occurred in 23 minutes after exposures at 2.4%, in 84 minutes after exposure at 1.3%, and in 135 minutes after exposure at 0.6%. Rabbits showed only eye and nose irritation when they were exposed at 1.3% for 30 or 90 minutes.

Mice and rabbits were also repeatedly exposed to mesityl oxide at 1.3% [55]. Ten mice were exposed for 15 minutes daily. After 5 exposures, none had died, and, after 11 exposures, 3 had died. When the exposures were increased to 30 minutes/day, all of 10 mice died within 6 days. Six rabbits showed only slight eye and nose irritation when they were exposed for 30 minutes/day for 15 days; however, when the exposures were increased to 60 minutes/day, the six rabbits developed spastic paralysis within 10 days and died 7-11 days after the paralysis was first observed.

The authors [55] also investigated the effects of mesityl oxide applied to the skin. Only 1 of 10 mice died when 0.1 ml of mesityl oxide was applied to the intact skin in the lumbar region; however, when 0.5 ml was applied, narcosis developed within 15 minutes, and death occurred in 3-9 hours.

Hart et al [55] found no significant abnormal changes by gross examination of the organs of mice that died after single exposures to mesityl oxide; however, mice that died after repeated exposures had necrotic spots in the liver, lung hemorrhages, and alimentary tract distention. Microscopic examination revealed necrosis, parenchymatous atrophy, and immature polynuclear cells in the liver. Some tubular degeneration in the kidneys and edema and hemorrhage in the lungs were also noted. Similar microscopic changes were found in rabbits after repeated exposures to mesityl oxide. The authors concluded that a concentration of about 0.7% of mesityl oxide was the maximum that could be inhaled by mice for an hour without fatal results. In rabbits, however, no deaths were observed at a concentration of 1.3%.

In 1942, Smyth et al [21] reported the effect on rats and guinea pigs after 6 weeks of 8-hour daily exposures (5 days/week) to mesityl oxide at 50, 100, 250, or 500 ppm (201, 402, 1,005, or 2,010 mg/cu m). Ten male Wistar rats and 10 guinea pigs of both sexes were used at each exposure concentration. No distinction was made between species in reporting the results because, according to the authors, the results differed only slightly. Nose and eye irritation was noted at the two higher exposure concentrations but not at 50 or 100 ppm. Exposure at 500 ppm was stopped after 10 days because of high mortality (13/20, 65%). No deaths occurred

in the groups exposed at 50, 100, or 250 ppm. Poor growth was noted in the survivors of the 250-ppm exposure but not in those exposed at 50 or 100 ppm. Blood changes were not apparent at any exposure concentration. Albumin was noted in the urine at the two higher concentrations but not at the lower two. Adverse liver and kidney changes were noted in all but the lowest exposure group. These changes increased proportionally with the dose. Liver damage was confined to congestion, but kidneys had dilated Bowman's capsules and swollen convoluted tubular epithelium. The lungs were often congested. The authors also determined that, in animals that died from the 500-ppm mesityl oxide exposures, the cause of death was the anesthetic effect on the circulatory and respiratory systems.

Smyth et al [21] supplemented their repeated-exposure studies by exposing rats and guinea pigs to mesityl oxide at high concentrations for short periods. At 13,000 ppm (52,130 mg/cu m), all 20 animals died after an exposure of 1 hour; at 2,500 ppm (10,050 mg/cu m), all the animals died after an 8-hour exposure; at 1,000 ppm (4,020 mg/cu m), 68% of the exposed animals died after 8 hours; and at 500 ppm, 30% died after 8 hours. Deaths resulted from narcosis; dead animals had some evidence of lung irritation.

The authors [21] concluded that mesityl oxide acted primarily as a narcotic. They also observed that, in rats and guinea pigs, "no effect whatever" was seen after 30 exposures to mesityl oxide for 8 hours at a concentration of 50 ppm.

In 1949, Carpenter et al [56] reported the results of an experiment to determine the extent of the acute toxicity of industrial compounds, including mesityl oxide. Groups of six male or female albino Sherman rats were exposed for 4 hours to compounds at successively higher concentrations

until two, three, or four of the animals died during a 14-day observation period. The investigators found that exposures to mesityl oxide at about 1,000 ppm (4,020 mg/cu m) killed two to four of the six rats in 14 days. They concluded that mesityl oxide should be considered a moderate hazard.

(8) Diacetone Alcohol

Lehmann and Flury [57] cited the results, but not the experimental details, of an unpublished study by E. Gross on the toxicity of diacetone alcohol. Repeated sc injections of 0.08 ml in rats caused exhaustion, but the animals recovered. Three rabbits given 2 ml of diacetone alcohol orally 12 times/day had kidney injury, slight narcosis, and albumin and sugar in the urine. One of the three rabbits died. Inhalation of diacetone alcohol at 2,100 ppm (9,975 mg/cu m) for 1-3 hours by mice, rats, rabbits, and cats caused restlessness, signs of irritation, head colds, and excitation followed by sleepiness. Rabbits also had kidney injury.

As was mentioned in the discussion of animal toxicity of acetone, there is evidence that diacetone alcohol caused earlier narcosis and a more constant depression of respiration in rats injected by vein than did acetone.

(9) Isophorone

Smyth et al [21], in 1942, described the toxicity of isophorone in rats and guinea pigs. Ten male Wistar albino rats (weighing 90-120 g) and 10 guinea pigs (weighing 250-300 g) were exposed to isophorone at concentrations, as determined by an interferometer, ranging from 25 to 500 ppm for 8 hours/day, 5 days/week, for 6 weeks. Weights were recorded weekly, blood cell changes were analyzed, and nose and eye

irritation was noted during exposures. Pooled urine samples were examined at least once, and microscopic examination was performed on selected animals.

The effects in the two species differed only slightly, with the rats being slightly more sensitive [21]. One animal exposed at an unknown but high concentration developed corneal necrosis. Chronic conjunctivitis and nasal irritation, sometimes followed by the appearance of a bloody exudate, were caused by repeated exposure to isophorone at a concentration of 500 ppm (2,825 mg/cu m) but not at 200 ppm (1,130 mg/cu m). Lungs were irritated by isophorone at unspecified concentrations. These concentrations produced congestion, capillary leakage, and desquamation of the epithelium that was not further described by the authors.

Growth was inhibited in all animals exposed to isophorone at concentrations of 100, 200, and 500 ppm (565, 1,130, and 2,825 mg/cu m) [21]. No blood cell changes were observed in animals exposed to isophorone at a concentration of 25, 50, 100, or 200 ppm (141, 282, 565, or 1,130 mg/cu m), although unspecified blood cell changes were noted in some animals exposed to isophorone at 500 ppm. Only animals exposed to isophorone at a concentration of 500 ppm excreted albumin in the urine. In addition, the urine of animals exposed to isophorone at a concentration of 500 or 200 ppm contained a substance that reduced Benedict's solution. The authors suggested that a detoxification product was responsible because isophorone alone did not reduce Benedict's solution.

Many animals exposed to isophorone had pale or brown kidneys, pale livers, congested spleens and lungs, and discolored bile [21]. However, exposure at 25 ppm produced neither microscopic abnormalities nor deaths.

Liver changes were reported in one of six animals exposed to isophorone at 50 ppm, in none of seven at 100 ppm, in none of six at 200 ppm, and in one of eight at 500 ppm. Kidney changes were found in four of six animals exposed at 50 ppm, in six of eight at 100 ppm, in four of seven at 200 ppm, and in six of nine at 500 ppm. No further information was provided on the liver and kidney changes.

All 20 animals survived exposure to isophorone at a concentration of 50 ppm, 2 of 16 died at 100 ppm, 3 of 18 died at 200 ppm, and 9 of 20 died at 500 ppm [21]. Animals that were killed by repeated exposure to isophorone had severely injured kidneys, lungs, or both. The kidneys of survivors were congested, and had dilation of Bowman's capsule and cloudy swelling in the convoluted tubules. Lungs were congested and had desquamation of bronchial epithelium sometimes followed by pneumonia. The liver was less affected than the lungs or kidneys, but it was congested with prominent Kupffer cells and cloudy swelling. The authors concluded that repeated exposure to isophorone had caused toxic effects, primarily on the kidneys and lungs, and that isophorone at 25 ppm caused no apparent adverse effects after exposures for up to 6 weeks. In an earlier study, Smyth and Seaton [58] found that single exposures to isophorone killed rats by narcosis, probably by paralysis of the respiratory center.

(b) Comparative Effects

In 1940, Specht et al [34] reported on an extensive study on the acute toxicity of a number of ketones in guinea pigs. In one series of experiments, five members of a homologous series--acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, and methyl n-amyl ketone--were compared. In another series of experiments, four six-carbon

ketones--methyl isobutyl ketone, methyl n-butyl ketone, cyclohexanone, and mesityl oxide--were compared. Measurements included rectal temperature, respiratory rate, and heart rate during each experiment. The authors attempted to correlate clinical signs and narcotic effectiveness with such physical properties as the number of carbon atoms, oil-to-water partition coefficients, and surface tension. The concentration of each ketone was determined by iodine titration, except for cyclohexanone, which was determined by titration of hydrochloric acid liberated after oxime formation.

Ten female guinea pigs of mixed stock weighing 400-600 g were exposed to the ketones at various concentrations and duration as shown in Table III-3 [34]. Ten unexposed guinea pigs served as controls. The clinical signs were reported during the experiments at only one representative concentration. Squinting, tearing, and rubbing of the eyes were considered to represent irritation of the cornea and conjunctiva, whereas sneezing, coughing, salivation, retching, and rubbing of the nose and mouth represented irritation of the buccal, nasal, and pharyngeal passages. These results, given in Table III-3, together with some apparently similar data developed by Specht and coworkers [59,60], suggest that irritative potency increases as the carbon number increases.

Specht et al [34] also reported that acetone produced immediate irritation at 50,000 ppm (118,500 mg/cu m) but no irritation at 10,000 ppm (23,700 mg/cu m). Methyl n-propyl ketone produced immediately an irritating effect at 2,500 ppm (5,925 mg/cu m) as well as at 10,000 ppm. Methyl ethyl ketone, however, produced immediate effects only at much higher concentrations. Methyl n-butyl ketone was even more irritating

TABLE III-3

IRRITATION IN GUINEA PIGS PRODUCED BY EXPOSURE TO KETONES

Ketone	Concentration (ppm)	Duration* (min)	Eyes		Upper Respiratory Tract			
			Tearing	Squinting	Salivation	Coughing	Rubbing of Nose	Nasal Discharge
Acetone**	20,000	25	1	1	0	-	0	-
Methyl ethyl ketone	25,000	10	2	3	3	-	2	-
Methyl n-propyl ketone	10,000	10	4	3	4	3	0	3
Methyl n-butyl ketone	6,000	15	4	4	4	2	4	1
Methyl n-amyl ketone	2,000	10	4	4	2	1	2	-
Methyl isobutyl ketone***	16,800	1	4	4	-	2	4	-
Cyclohexanone	4,000	10	4	4	4	-	0	2
Mesityl oxide	5,000	5	4	4	4	4	4	-

Key: 0=negative, 1=slight, 2=moderate, 3=marked, 4=extreme
*Observed effects may have occurred at any time during exposure up to time indicated.

**Adapted from reference 60
***Adapted from reference 59
Data on other ketones adapted from reference 34

than methyl n-propyl ketone, producing immediate irritation at concentrations as low as 1,200 ppm. Immediate, strong effects were also noted with methyl n-amyl ketone and mesityl oxide at all concentrations tested. Immediate irritation was not found below concentrations of 10,000 ppm for methyl isobutyl ketone, but it occurred at all concentrations tested above 10,000 ppm. The authors also noted that methyl n-butyl ketone and cyclohexanone produced a clouding of the cornea that persisted beyond the exposure period, but they did not mention whether or not it abated.

In addition to the irritant effects noted above, Specht et al [34] reported that the ketones used in this study produced narcosis, CNS depression, and respiratory dysfunction. These data are summarized in Table III-4. The values depicted represent the product of the exposure concentration and the duration of exposure (Ct product) calculated from the data presented by Specht et al. The criterion for a particular effect's being significant was arbitrary. In this case, a decrease of 30 breaths/minute, 50 heartbeats/minute, or body temperatures 4 C below controls was considered significant. The first reported time at which this decrease occurred was then multiplied by the concentration of the ketone.

The data in Table III-4 suggest that, as the number of carbon atoms in these ketones increases, there is generally a decrease in the Ct product to produce a particular toxic effect. Although there are Ct products that do not fit into this model, the general trends suggest that CNS depression increases with increasing carbon numbers. Methyl n-amyl ketone was aberrant in this respect, probably because it was not lethal at this concentration. The Ct of methyl n-amyl ketone for the first death at 5,000

TABLE III-4

Ct* PRODUCTS FOR KETONES
(X 1,000)

Ketone Name	Concentration (ppm)	No. of Carbon Atoms	First Death**	Respiration	Pulse Rate	Rectal Temperature	Reference
Acetone	20,000	3	26,800 (1)	4,800	4,800	10,800	60
Methyl ethyl ketone	25,000	4	4,500 (1)	750	2,250	3,750	34
Methyl n-propyl ketone	10,000	5	5,100 (3)	350	1,400	1,400	34
Methyl n-butyl ketone	6,000	6	2,400 (2)	780	360	780	34
Methyl n-amyl ketone	18,100	7	No deaths in 890 min***	90	1,720	1,720	34
Cyclohexanone	4,000	6	No deaths in 355 min	120	1,320	1,320	34
Methyl isobutyl ketone	18,000	6	1,428 (1)	420	622	1,008	59
Mesityl oxide	5,000	6	1,950 (2)	300	1,200	1,200	34

*Ct product units in ppm-minutes
**Product unit at which first death occurred; number of deaths in parentheses
***Product was 1,400 at 5,000 ppm

ppm (a concentration not described in detail by Specht et al [34]) was calculated as 1,400 x 10^3 ppm-minutes, a value that agrees with the above observation that carbon number and mortality are directly related.

In Table III-4, there is evidence that the relationship of mortality, CNS effects, and respiratory dysfunctions with carbon number may also apply to those six-carbon ketones (mesityl oxide, cyclohexanone, methyl isobutyl ketone) that are not straight chain ketones. Although there appears to be little correlation between the type of rearrangement (cyclization, unsaturation, or branching) and the Ct product, the Ct products are generally less than those of the five-carbon ketone, methyl n-propyl ketone. However, when these Ct products are compared with those of methyl n-butyl ketone, there are many discrepancies.

Selected animals from each exposure group were killed and examined to determine macroscopic and microscopic adverse effects on organs and tissues [34]. Occasional scattered liver cells containing fat droplets were found in a few animals. Congested liver capillaries were found in animals exposed to each of the ketones except acetone. The authors concluded that, in general, few or no significant changes were found in the liver. Each of the ketones produced slight to marked congestion of the interalveolar capillaries in the lungs. Various degrees of congestion of the interstitial capillaries of the kidneys were found in all guinea pigs. Hemorrhaging was found in the pulp of the spleen of all animals, and it was usually perifollicular in those exposed to acetone. Hemosiderosis was frequently found. Congestion of the capsular capillaries of the adrenal glands occurred in all animals except those exposed to acetone. Extravasation of red blood cells into the adrenal gland occurred in animals

exposed to methyl n-butyl ketone and methyl n-propyl ketone at 40,000 ppm. Fat droplets were present in adrenocortical cells of all animals. Congestion of the pia-arachnoid vessels and capillaries of the cerebral cortex occurred in guinea pigs exposed to methyl n-butyl ketone. The brains of other animals were not examined. No microscopic changes were observed in the heart, stomach, or pancreas.

Specht et al [34] concluded that there was no marked variation among the animals exposed to various ketones. The most consistent observation was congestion, and the organs most affected, in decreasing order, were lungs, kidneys, spleen, adrenals, and brain. Distention of renal tubules was also common, but liver congestion was considered negligible. Specht et al concluded that all of the ketones studied produced a general, progressive narcosis that best correlated with the partition coefficient between olive oil and water. Mesityl oxide was somewhat aberrant in this respect. All of the ketones produced irritation of mucous membranes and a transient reflex depression of the respiratory and heart rate that furnished a limiting index for adequate warning properties during inhalation.

Specht et al [34] presented olive oil-to-water partition coefficients for eight of the ketones. A comparison of these partition coefficients with LD50's for the ketones is given in Table III-5. Since factors such as the sex and strain of the rats used sometimes differed for the compounds tested, a detailed comparison of the LD50's is not valid.

TABLE III-5

COMPARISON OF PARTITION COEFFICIENTS
OF KETONES WITH LD50's

Ketone	Partition Coefficient* (oil to water)	Oral LD50 in Rats (g/kg)	Sex	Reference
Acetone	0.1	8.5	F	61
Methyl ethyl ketone	1.9	5.5	F	61
Methyl n-propyl ketone	16.6	3.7	M	61
Methyl n-butyl ketone	26.5	2.6	M	62
Methyl n-amyl ketone	42.2	1.7	F	61
Methyl isobutyl ketone	20.6	2.1	M	63
Cyclohexanone	24.1	1.5	M	64
Mesityl oxide	4.6	1.1	-	65

*Adapted from reference 34

It appears that lipophilicity and oral toxicity are directly related for the five homologous ketones. As the affinity of the ketone for the oil increases, the oral toxicity correspondingly increases. The correlation is not applicable to the nonlinear six-carbon ketones.

(c) Effects on the Skin and Eyes

Smyth et al [61,62] studied primary skin irritation produced by a number of ketones on rabbits. The authors scored the reactions produced on the clipped skin of five albino rabbits within 24 hours of application of 0.01 ml of undiluted ketone or of dilutions in water, n-propylene glycol, or kerosene. Each ketone was graded according to its irritant effect. Grade 1 produced the least visible capillary congestion in undiluted form, grade 6 produced necrosis when undiluted, and grade 10 produced necrosis from a 0.01% solution.

The grades found for the ketones were acetone, 1; methyl ethyl ketone, 2; methyl n-propyl ketone, 1; methyl n-amyl ketone, 4; methyl isoamyl ketone, 1 [61]; and methyl n-butyl ketone, 1 [62]. Further experimental details or results were not presented.

The effects of acetone and of cyclohexanone on the eyes have been studied by Rengstorff et al [66]. In one experiment, 0.5 ml of either ketone was applied to the clipped skin on the back of albino guinea pigs. Four additional guinea pigs were given sc injections of 0.05 ml of a 1:1 mixture of either ketone in saline, and 12 more were injected sc with 0.05 ml of 5% of either ketone in saline. Guinea pigs were injected with acetone or cyclohexanone three times/week for 3 weeks. Eyes were examined 60 or 90 days after the initial application of the ketone and then every 30 days for up to 6 months after the experiment began. As a control, the eyes of over 500 other guinea pigs from the same colony were examined.

Cataracts developed in guinea pigs given acetone or cyclohexanone either by injection or dermal application [66]. Of the 12 guinea pigs given acetone cutaneously for 3 weeks, two developed cataracts by the 3rd

month. Cutaneous administration of cyclohexanone produced cataracts, which were first seen in the 5th or 6th month in 3 of 12 guinea pigs. Subcutaneous administration of acetone and cyclohexanone caused cataracts to form in 7 of 16 and 2 of 16 exposed guinea pigs, respectively. Generally, the cataracts in these guinea pigs were first seen by the 3rd month and were still apparent in later examinations. However, lens damage was occasionally reversed within 3 months after being observed. No cataracts formed in the control guinea pigs. Microscopic examination of a guinea pig that developed cataracts after cutaneous exposure to acetone showed extensive lens damage. Eosinophilic deposits were found in the subcapsular areas of the lens, and the lens epithelium could not be distinguished from the capsule. The eyes of a control guinea pig showed no abnormal features.

In a second experiment, two guinea pigs of each sex and one rabbit were given 1 ml of acetone cutaneously two times/day, 5 days/week for 4 weeks, and an equal number of animals were given acetone for 8 weeks [66]. Four guinea pigs and two rabbits were given saline cutaneously and four unexposed guinea pigs served as controls. The animals' eyes were examined once a week for 8 weeks and then every other week until 6 months after the initial exposure. Cutaneously applied acetone produced cataracts in guinea pigs but not in rabbits. Two of the eight exposed guinea pigs had bilateral cataracts, while none of the controls had lens defects. It cannot be determined whether the negative findings were caused by the small number of animals used or by the rabbit being less sensitive to the ocular effects of acetone. However, these studies demonstrated the ability of acetone and cyclohexanone to produce cataracts in albino guinea pigs.

Carpenter and Smyth [67] studied the effects on the rabbit cornea of a large number of chemical agents, including acetone, diisobutyl ketone, cyclohexanone, mesityl oxide, diacetone alcohol, and isophorone. A ranking system from 1 to 10 was used by the authors to numerically score the extent of ocular damage. In a typical experiment, a variable amount of the substance was applied to the center of the corneas of normal albino rabbits. Eighteen to 24 hours later, the eye was examined in strong diffuse daylight, and damage to the corneas and irises was scored. The eye was then stained with fluorescein to determine the extent of necrosis. A score of 5 represented severe injury. This score corresponded to necrosis covering 75% of the cornea after staining or more severe necrosis covering a smaller area. The volume of the test substance also affected the score.

The authors [67] assigned an injury grade of 1 to diisobutyl ketone, a grade of 4 to isophorone, and a grade of 5 to acetone, cyclohexanone, mesityl oxide, and diacetone alcohol. Substances such as acetic anhydride and sulfuric acid (5% solution) had grades of 9, and sodium hydroxide (1% solution) had a grade of 10.

Truhaut et al [68] studied the effects of isophorone on the eyes of rabbits. The official procedure of the US Food and Drug Administration was used for this investigation (Federal Register 29:13009, September 16, 1964), except that Bourgogne rabbits were used instead of albino rabbits. This procedure, described earlier by Draize and coworkers [69], consists of instilling 0.1 ml of the test compound into the eyes of six rabbits. The eyes are then examined and the degree of injury is noted after 24, 48, and 72 hours. Either ulceration, or opacity of the cornea, inflammation of the iris, and conjunctival swelling are considered positive reactions. A test

is considered positive if four or more animals have a positive reaction. An acute ocular index rating with a maximum value of 110 is then derived [69].

Truhaut and coworkers [68] reported that four rabbits had pronounced opacity of the cornea which extended over the entire surface. All rabbits had inflammation of the eyelids and conjunctiva accompanied by a pronounced purulent discharge. Microscopic examination showed that the corneal epithelium was frequently reduced or nonexistent and sometimes had signs of ulceration. Inflamed cells in the cornea were also observed. Accordingly, the authors judged isophorone to be a moderate eye irritant. They assigned an acute ocular irritation rating of 20/110 to isophorone.

(d) Effects on the Nervous System

Mendell et al [70] exposed rats, cats, and chickens to methyl n-butyl ketone to observe its effects on the peripheral nervous system. Four Sprague-Dawley rats and four domestic cats were initially exposed to methyl n-butyl ketone at 600 ppm (2,460 mg/cu m), 24 hours/day, 7 days/week, for up to 12 weeks. Chickens were initially exposed at 200 ppm (820 mg/cu m). Exposures were later adjusted to 100 ppm (410 mg/cu m) for chickens and to 400 ppm (1,640 mg/cu m) for rats and cats to minimize complications from starvation and weight loss. Environmental conditions in the exposure chamber were maintained at a normal atmosphere. Methyl n-butyl ketone concentrations were monitored by gas chromatography. Pair-fed animals were used as the controls. Electromyographic studies were performed weekly on all cats exposed to methyl n-butyl ketone. The electromyograms were recorded from several muscles, eg, the supraspinatus, triceps, and extensor carpi, with monopolar electrodes. At the end of the experiment, exposed

animals and an equal number of control animals were killed, and selected muscles were examined by light microscopy. Thin sections of the sciatic nerve were examined by electron microscopy.

All the exposed animals developed peripheral neuropathy during the exposure [70]. The earliest sign of peripheral neuropathy in chickens was the inability to stand at 4-5 weeks. Cats dragged their limbs at 5-8 weeks and later had forelimb weakness. Rats dragged their hindlegs at 11-12 weeks. Exposed rats greatly increased their water intake.

Between 4 and 6 weeks, electromyographic examination of all exposed cats showed abnormal insertional activities accompanied by positive waves [70]. Fibrillation potentials appeared in their muscles while they were at rest and accompanied insertional activity during the 9th and 10th weeks. In all exposed cats, the ulnar nerve conduction velocity was decreased between 7 and 9 weeks to an average of 50 meters/second. (Normal velocity in that laboratory was 115.) The electromyographic changes occurred in all the muscles tested. Although a few polyphasic potentials were seen at 8-9 weeks, the amplitude of motor unit action potentials did not differ significantly from that of controls.

The authors [70] concluded that peripheral neuropathy had been induced in all three species exposed to methyl n-butyl ketone at 100-600 ppm (410-2,460 mg/cu m) for 1,440 hours (24 hours/day for 2 months). This conclusion correlated well with their earlier finding that peripheral neuropathy developed in workers exposed to methyl n-butyl ketone for 1,584 hours (22 days/month, 8 hours/day, for 9 months). They also concluded that the neuropathy observed in the animals was similar, according to clinical criteria, to that seen in affected workers who used methyl n-butyl ketone.

In both cases, the neuropathy involved predominantly motor or muscular weakness, and the nerve conduction velocity decreases noted in humans were also seen in the exposed animals.

Spencer et al [71] studied the effects of methyl n-butyl ketone and methyl isobutyl ketone on adult rats. Six rats were exposed to each ketone for 6 hours/day, 5 days/week, for 4 months. Three rats served as controls. The concentration of methyl n-butyl ketone in the exposure chamber was calculated as 2,000 ppm (8,200 mg/cu m) and determined to be 1,300 ppm (5,330 mg/cu m) when analyzed by gas-liquid chromatography. The concentration of methyl isobutyl ketone in the exposure chamber was measured at 1,500 ppm (6,150 mg/cu m) by gas-liquid chromatography; the authors noted that approximately 3% methyl n-butyl ketone was present as a contaminant. The rats were examined periodically for signs of neurologic effects. After the 4-month exposure, the rats were killed, and various nerve tissues were examined microscopically.

Slight narcosis was observed after 4 hours of exposure to methyl n-butyl ketone, and some loss of coordination was noted after 5.5 hours of exposure [71]. Slow progressive weight loss was evident from the 73rd day of exposure to the end of the exposure period. Animals developed symmetrical hindleg footdrop between the 3rd and 4th months of exposure. Severely affected rats also exhibited proximal hindleg and foreleg weakness.

Microscopic examination showed a consistent distribution of peripheral and CNS damage [71]. Degeneration of the peripheral nerve fibers was most evident in the intramuscular and distal portions, although scattered changes were evident in the sciatic nerve up to the level of the

dorsal root ganglia. The authors noted that the most prominent early nerve fiber abnormality was an axonal dilatation associated with localized fiber swelling. Longitudinal sections of nerve fibers and teased fibers showed focal, internodal, paranodal, or nodal axonal swellings. Neither internodal demyelination nor remyelination was observed.

Animals exposed to methyl isobutyl ketone for 4 months showed a normal rate of weight gain, a slight narcosis during exposure, and no signs of neurologic dysfunction [71]. Microscopic examination of CNS tissues and proximal parts of the peripheral nervous system was insignificant. Frank distal nerve fiber degeneration was not observed. However, the most distal sections of the ulnar and tibial nerves had many axons with dilated mitochondrial remnants, adaxonal Schwann cell invaginations, and case focal swellings. The authors concluded that methyl isobutyl ketone was relatively ineffective in producing neurologic dysfunction. They noted that the minimal neuropathic changes induced by methyl isobutyl ketone may be related to the presence of the 3% methyl n-butyl ketone as a contaminant of the methyl isobutyl ketone used in this study.

This study [71] showed that, at a methyl n-butyl ketone concentration of 2,000 ppm, there was a progressive, symmetrical, distal neuropathy that spread proximally with time. The minimal neuropathic changes induced by methyl isobutyl ketone were most probably related to methyl n-butyl ketone, which was a contaminant.

In 1975, Raleigh and coworkers [72] reported on the toxicity of methyl n-butyl ketone in cats. Cats were exposed to methyl n-butyl ketone at 100 or 330 ppm (410 or 1,353 mg/cu m) for 6 hours/day, 5 days/week for approximately 5 months. No evidence of clinical neuropathy was observed.

However, minimal microscopic changes were observed in nerve fibers supplying the interosseous muscle of cats that were exposed at 330 ppm for about 4.5 months. No microscopic changes were found in cats exposed at 100 ppm.

In other studies, the authors [72] reported that neuropathy was produced in cats that were injected twice daily sc with 150 mg/kg of methyl n-butyl ketone, 5 days/week, for 2 months and in dogs that were injected twice daily sc with 150 mg/kg of methyl n-butyl ketone, 5 days/week, for 2-4 months. No clinical neuropathy was seen in guinea pigs that had unreported amounts of methyl n-butyl ketone applied to the skin repeatedly for about 8 months.

In 1976, Saida et al [73] studied the effects of methyl n-butyl ketone on the nervous system of rats and the effects of methyl ethyl ketone on methyl n-butyl ketone toxicity. The authors [73] studied two groups of Sprague-Dawley rats. In the first group, 12 rats weighing 190-210 g were exposed to methyl n-butyl ketone vapor at a concentration of 400 ppm continuously (24 hours/day, 7 days/week), the concentrations being monitored by the gas chromatographic method of Mendell and colleagues [70]. They were serially killed and examined microscopically for neurologic changes. In the second group, 12 rats each weighing 160-180 g were continuously exposed to methyl n-butyl ketone at a concentration of 225 ppm (922 mg/cu m), to methyl ethyl ketone at 1,125 ppm (3,319 mg/cu m), or to a combination of methyl n-butyl ketone at 225 ppm and methyl ethyl ketone at 1,125 ppm. These rats were also serially killed and examined microscopically for neurologic changes. Control animals held under similar conditions were not exposed. A number of rats exposed to methyl n-butyl

ketone at 400 ppm (1,640 mg/cu m) were killed on the 16th, 28th, and 42nd days, and rats exposed at 225 ppm were killed on the 16th, 25th, 35th, 55th, and 66th days.

Paralysis occurred 42 days after exposure to methyl n-butyl ketone at 400 ppm and 66 days after exposure to methyl n-butyl ketone at 225 ppm [73]. The authors reported that an increase in the number of neurofilaments and inpouching of the myelin sheath were apparent many weeks before the onset of paralysis. In animals exposed to methyl n-butyl ketone at 400 ppm for 16 days, the number of neurofilaments significantly increased and had increased further when measured after 42 days of exposure. In addition, after 42 days of exposure to methyl n-butyl ketone at 400 ppm, rats had significantly fewer neurotubules ($P<0.01$) than did controls.

The authors [73] reported that the number of inpouchings of myelin sheaths in individual teased nerve fibers was strongly correlated with the duration of exposure. In the late stages of neuropathy when the animals were paralyzed, the authors occasionally observed Wallerian degeneration of nerve fibers.

To determine the earliest site of damage, Saida et al [73] studied the anterior horn cells, nerve roots, nerve trunks, intramuscular nerves, and motor endplates. No abnormalities were found in the motor endplates or intramuscular nerves of the intrinsic foot muscles in rats exposed to methyl n-butyl ketone at 225 ppm for 16 days or to a combination of methyl n-butyl ketone and methyl ethyl ketone at 225:1,125 ppm for 16 days. However, rats exposed to the combination did have more neurofilaments and inpouchings of the myelin sheath of the sciatic nerve. After 25 days of

exposure to the combination, similar changes in the nerve roots and intramuscular nerves were noted when clinical paralysis was present, but no abnormalities were observed in the axon terminals or postsynaptic membrane at the neuromuscular junction. After 66 days of exposure to methyl n-butyl ketone at 225 ppm, rats had denervation of motor endplates. No abnormalities were observed in anterior horn cells and dorsal root ganglion cells.

When the authors [73] compared the effects of methyl n-butyl ketone at 225 ppm, of methyl ethyl ketone at 1,125 ppm, and of the two substances combined at a ratio of 225:1,125 ppm, they noted striking differences in toxicity. With methyl ethyl ketone alone at 1,125 ppm, no peripheral neurotoxicity occurred in rats for up to 55 days; additional exposure for up to 5 months did not produce abnormalities. Rats exposed to methyl n-butyl ketone at 225 ppm did not develop paralysis until they had been exposed for 66 days. However, rats exposed to the combination developed paralysis after 25 days of exposure. The authors noted that the time of onset of inpouchings of myelin sheaths, axonal swelling, and denudation of axons was greatly shortened in rats exposed to the combination. The authors concluded that the earliest microscopic change produced by methyl n-butyl ketone was an increase in the number of neurofilaments in large myelinated nerve fibers. Axonal swelling and myelin thinning occurred with longer exposures. Inpouchings of the myelin sheath also occurred early in neuropathy and increased in number as exposure continued.

These studies show that methyl ethyl ketone alone at 1,125 ppm did not produce peripheral neuropathy in rats after repeated exposure.

However, methyl ethyl ketone shortened the latency period of the onset of methyl n-butyl ketone-induced peripheral neuropathy.

Spencer and Schaumburg [74] studied the effects of repeated sc injections of three ketones individually and in combination. Each cat was injected twice daily with 150 mg/kg of the test substances. Eight cats were injected with undiluted methyl n-butyl ketone, six with methyl ethyl ketone, four with methyl isobutyl ketone, four with a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone, and six with a 9:1 mixture of methyl ethyl ketone and methyl isobutyl ketone for 5 days/week for up to 8.5 months. Four cats received twice-daily injections of an equivalent volume of saline, and three other cats given no injections were used to study normal tissue.

Two series of 20 biopsies were performed on some cats [74]. Tissue samples were taken from the right hindfeet after 45 days and from the left hindfeet after 135 days. Tissues sampled at biopsy included pacinian corpuscles, branches of the lateral plantar nerves, and portions of a superficial interosseous muscle.

Morphologic studies were conducted on three cats that received methyl n-butyl ketone for 2, 4, and 6 months [74]. The tissues sampled were the pacinian corpuscles in hindfeet, the sciatic, tibial, peroneal sural, and plantar nerves in the hindlegs, the proximal and distal hindleg muscles, the lumbosacral dorsal root ganglia and corresponding dorsal and ventral roots, and multiple levels of the spinal cord and medulla oblongata.

The authors [74] reported that the cats often salivated excessively and showed signs of narcosis shortly after injections. Abscesses and skin ulcers appeared at the injection site in several animals. All 10 cats

receiving injections of methyl ethyl ketone or a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone died after 31-93 days. Two cats receiving injections of methyl n-butyl ketone alone died after 7 and 93 days. The cats given methyl isobutyl ketone did not die.

Spencer and Schaumburg [74] detected neurologic dysfunction only in cats that were given methyl n-butyl ketone alone. The first sign of peripheral neuropathy was a weakness of the hindquarters after 8-10 weeks of methyl n-butyl ketone injections. After 10-12 weeks, the cats had severe hindleg footdrop and, by 16 weeks, they could not walk. Cats injected with methyl ethyl ketone, methyl isobutyl ketone, or 9:1 mixtures of methyl ethyl ketone with methyl n-butyl ketone or methyl isobutyl ketone had no neurologic dysfunction.

Cats given methyl n-butyl ketone and a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone had nerve fiber damage [74]. Tissues from the cats given the other ketones appeared normal. Cats given methyl n-butyl ketone for 45 days had a proliferation of neurofilaments in pacinian corpuscles with subsequent degeneration of axoplasm. After 135 days, pacinian corpuscles were either denervated or had extensive axonal damage. Focal giant axonal swelling was seen in plantar nerves and interosseous muscles. No changes were apparent in hindleg tissues from cats that received a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone for 45 and 135 days; however, after 8.5 months, tibial nerve branches contained abnormal numbers of fibers that had segmental remyelination. Pacinian corpuscles appeared normal.

The peripheral and central nervous systems were studied in three cats that received methyl n-butyl ketone for 2, 4, and 6 months [74]. One cat

given injections for an unspecified period had no signs of neurologic dysfunction, but parts of its peripheral nervous system showed changes characteristic of neuropathy induced by methyl n-butyl ketone. The other two cats had overt signs of neuropathy. There was microscopic evidence in the cat that was treated for 4 months, but the authors discussed both cats in general. The cats had nerve fiber degeneration, proximal muscle fiber atrophy, and axonal swellings in the sciatic nerve. Giant axonal swellings of myelinated fibers, enlargement of nerve terminals, and total fiber breakdown were found in the CNS.

Spencer and Schaumburg [74] concluded that methyl n-butyl ketone produced a primary axonal degeneration that affected the distal regions of nerves first and then progressed proximally. To describe this pattern, they referred to an earlier study [75] in which they proposed the term "central-peripheral distal axonopathy."

They [74] found microscopic evidence of neuropathy in cats that received a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone. They noted that this subclinical damage appeared to be caused by methyl n-butyl ketone in the amount given (15 mg/kg), but they also pointed out that, as reported by Saida et al [73], methyl ethyl ketone may have potentiated the toxicity of methyl n-butyl ketone.

This study [74] further confirmed that methyl n-butyl ketone is a neurotoxic agent. It also showed that repeated administration of only methyl ethyl ketone produced no clinical or microscopic evidence of neuropathy. Repeated injections of methyl isobutyl ketone of 98.8% purity and of a 9:1 mixture of methyl ethyl ketone and methyl isobutyl ketone also produced no clinical or microscopic evidence of neuropathy. These findings

confirm the suggestions of Spencer et al [71] that the subclinical plantar nerve damage in rats exposed to commercial grade methyl isobutyl ketone for up to 5 months was probably caused by 3% methyl n-butyl ketone in the methyl isobutyl ketone used for this study.

Krasavage et al [76] also found neurotoxic effects of methyl n-butyl ketone. Two groups of 18 male Sprague-Dawley rats were exposed at vapor concentrations of 100 and 330 ppm for 6 hours/day, 5 days/week, for 72 weeks. Beginning at 4 weeks and continuing at about 6-week intervals for the first 52 weeks, rats were killed and examined by light and electron microscopy.

Neuropathy (hindlimb weakness and microscopic evidence of nerve damage) was seen only in rats that were exposed at 330 ppm (1,353 mg/cu m) [76]. This first appeared in 1 rat after 149 exposures. Although weight gain was depressed in both groups, no evidence of neurotoxicity, either clinical or microscopic, was observed at 100 ppm.

DeJesus et al [77] studied the effects of methyl n-butyl ketone and methyl ethyl ketone on peripheral nerves of Wistar rats. Animals were exposed for 6 hours/day, 5 days/week to methyl n-butyl ketone vapor at 60 ppm (246 mg/cu m) for 6 weeks, and at 100 ppm (410 mg/cu m) for 4 weeks, and at 1,050 and 1,450 ppm (4,305 and 5,945 mg/cu m) for 5 weeks. Rats were also exposed to methyl ethyl ketone vapor at 2,150 ppm for 6 weeks and at 4,740 ppm (13,983 mg/cu m) for 4 weeks.

Rats exposed to methyl n-butyl ketone at 1,050 and 1,450 ppm developed typical signs of peripheral neuropathy. These signs were hindleg dragging, decreased motor conduction velocities in sciatic nerves, decreased evoked muscle action potentials, and weight loss. Rats exposed

to methyl ethyl ketone at 2,150 and 4,740 ppm and rats exposed to methyl n-butyl ketone at 60 and 100 ppm had no signs of peripheral neuropathy.

Schaumburg and Spencer [78] studied the effects on the hypothalamus and optic nerve tract of cats given 2,5-hexanedione, a compound suggested to be a neurotoxic metabolite of methyl n-butyl ketone. Four young adult cats were given 0.5% 2,5-hexanedione in their drinking water for up to 136 days and then were perfused with a fixative. Two untreated cats served as controls. After 60-75 days, cats had an unsteady gait and distal weakness in the lower extremities. Further treatment produced a progressive symmetrical weakness with footdrop. At the time of perfusion, cats were quadriparetic and unable to walk. Visual loss, abnormal pupillary reflexes, nystagmus, staggering, and hoarseness were not observed.

The authors [78] found evidence of giant axonal degeneration that was similar to the findings of other investigations [71,74]. They also found advanced distal fiber degeneration in the rostral gracile, dorsal spinocerebellar, and caudal corticospinal tracts. In contrast, early axonal swellings were found throughout the mammillary bodies, the lateral geniculate body and distal optic tract, and the superior colliculus that were not associated with necrosis, macrophage accumulation, or hemorrhage. The optic nerves, vestibular nuclei, dorsal medial thalamic nuclei, and inferior colliculi were normal. The authors suggested that these changes might be responsible for the alterations of memory and vision that have occasionally been reported in n-hexane neuropathy. They thought that CNS degeneration might be irreversible.

Goldberg et al [79] studied modifications to behavior in rats induced by inhalation of vapors from several industrial solvents, including

acetone. Conditioned avoidance and escape in a modified pole-climbing test were the two behavioral patterns observed. Rats were trained to climb the pole within 2 seconds after receiving a stimulus. Any delay of response greater than 6 seconds was considered a significant change in behavior.

Female CFE rats, weighing 140-180 g, were selected for exposure according to their training performance in the behavioral testing apparatus before exposure [79]. The rats, in groups of 8-10, were exposed at nominal concentrations of 3,000, 6,000, 12,000, and 16,000 ppm (7,110, 14,220, 28,440, and 37,920 mg/cu m). The actual concentrations, as determined by an interferometer, were found to be within 10% of these concentrations. Rats were exposed for 4 hours/day, 5 days/week, for 2 weeks, and tested for performance before and after each exposure. Rats exposed to acetone at concentrations above 3,000 ppm showed some behavioral changes, but no alteration of avoidance or escape behavior was observed in rats exposed at 3,000 ppm [79]. At 6,000 ppm 38% of the rats showed an inhibition of avoidance behavior after the 1st day of exposure and 25% after the 2nd day, but no decrement was reported after the remaining exposures. None of the animals exposed at this concentration showed decreased escape behavior. After the first exposure at 12,000 ppm, 50% of the rats showed inhibited avoidance response and 12% showed inhibited escape response. After the second exposure, avoidance response was inhibited in 37%, but the escape response was no longer inhibited. After three exposures, the avoidance response was inhibited in 25% of the rats, and no further inhibition occurred after additional exposures. Several rats exposed at 12,000 or 16,000 ppm developed muscular incoordination after one exposure; however, no signs of muscular incoordination were noted after subsequent exposures.

Of the rats exposed at 16,000 ppm, 62% had an inhibition of the avoidance response after one exposure. The escape response was inhibited in 25% of these animals after one exposure; however, as in the previous group, no inhibition was observed on subsequent days. The avoidance response was inhibited in 37% of the rats after 2 exposures, in 37% after 3 exposures, and in 25% after 4, 5, and 10 exposures. The inhalation of acetone did not significantly affect the growth rate of exposed animals compared to control rates.

Goldberg and coworkers [79] showed that acetone at concentrations of 6,000 ppm or more modified avoidance and escape in rats. Many of the rats exposed at 12,000 and 16,000 ppm developed tolerance, and escape responses were less inhibited than avoidance responses by exposure to acetone. Inhalation of acetone at increasing concentrations produced modification of behavior in an increasing proportion of the experimental population.

Johnson et al [80] studied the effects of methyl n-butyl ketone on behavior and the nervous system. Groups of 10 albino male rats and 8 male monkeys were exposed to methyl n-butyl ketone at 97 or 976 ppm (398 or 400 mg/cu m) for 6 hours/day, 5 days/week. Similiar but unexposed groups of rats and monkeys served as controls. For neurologic tests in rats and monkeys, maximum motor conduction velocities, absolute refractory period, and muscle action potentials were recorded. In addition, electroencephalograms and visually evoked potentials were recorded from monkeys.

For behavioral studies, 12 Sprague-Dawley albino rats were trained on a multiple fixed ratio 5, fixed interval 3-minute schedule (mult FR5FI3) [80]. Six standard operant test enclosures with a press bar, food cup, and

feeder were used. A red light was associated with the fixed ratio and a yellow light with the fixed interval of the operant schedule. Inter-response times were recorded separately from each component of the multiple schedule of reinforcement. Stability in responding was reached after 20-40 days of training. For recovery studies, three monkeys from each exposed group were neurologically tested monthly until recovery was evident. Motor conduction velocity in the sciatic tibial nerve was the measurement used to evaluate neurologic recovery because, as the authors stated, it had given the earliest indication of methyl n-butyl ketone-induced neurotoxicity at both exposure levels.

After 25 weeks of exposure to methyl n-butyl ketone at 976 ppm the experiment was terminated because hindlimb drag was evident in both rats and monkeys [80]. The authors reported that exposure at 976 ppm reduced motor conduction velocities in ulnar and sciatic-tibial nerves, decreased the evoked muscle action potentials, lengthened implicit time of visually evoked potentials, impaired operant behavioral performance, and reduced body weight.

In monkeys, the first significant decrease in motor conduction velocity occurred after 4 months of exposure at 976 ppm [80]. At 97 ppm, the first significant decrease in motor conduction velocity occurred after 9 months. In rats exposed at the higher concentration, a significant decrease in motor conduction velocity occurred after 13 weeks.

Operant behavior in rats exposed at 976 ppm first appeared to be significantly impaired after 2 weeks [80]. No effects on operant behavior were found after exposure at 97 ppm.

The study of Johnson et al [80] is in agreement with the findings of other investigators [70-72,74] on the neurotoxicity of methyl n-butyl ketone. An interesting finding was the impaired operant behavior after 2 weeks of exposure at 976 ppm because other measurements indicated that 21 weeks of exposure was necessary to produce detectable nerve damage. These findings are consistent with a suggestion that modification of behavior might occur in humans exposed to methyl n-butyl ketone before the onset of peripheral neuropathy.

Anger and coworkers [81] described, in a report available only as an abstract, the effects of methyl n-amyl ketone by inhalation exposures and ip injections on multiple fixed ratio, fixed interval (MULT FRFI) response rates in rats. Twelve rats were injected intraperitoneally (ip) with methyl n-amyl ketone at 18, 37, 74, and 175 mg/kg and were tested 15 minutes after treatment.

At 18 mg/kg, there was little effect on the fixed interval response rate, a moderate decrease in FI rate at 37 and 74 mg/kg, and a near cessation of responding at 175 mg/kg. Changes were statistically significant at 37, 74, and 174 mg/kg. Inhalation exposures to methyl n-amyl ketone at concentrations in excess of 1,600 ppm (7,472 mg/cu m) had effects similar to those in animals that were injected with 175 mg/kg.

Johnson et al [82] described an electrodiagnostic study of the neurotoxicity of methyl n-amyl ketone. Rats and monkeys were exposed to methyl n-amyl ketone at 0, 131, and 1,025 ppm (612 and 4,787 mg/cu m) for 6 hours/day, 5 days/week for 9 months. Conventional procedures were used throughout the study. None of the animals showed any clinical signs of illness during the course of the study. No impairment in locomotion,

grip, or gait was observed. Electrodiagnostic studies in the form of maximum motor conduction velocities in sciatic-tibial and ulnar nerves in all exposed animals did not differ significantly from those of controls. Microscopic examination revealed no tissue damage.

This study [82] provides evidence that methyl n-amyl ketone is not neurotoxic. Because methyl n-amyl ketone is one of the two closest homologs of methyl n-butyl ketone, methyl n-propyl ketone being the other, this evidence suggests that the straight-chain 6-carbon structure is essential for producing neurotoxic effects.

(e) Metabolism

The metabolic pathways for the degradation and biotransformation of the ketones are not completely understood. Several intermediates and endproducts have been identified for methyl n-butyl ketone, methyl ethyl ketone, methyl isobutyl ketone, and cyclohexanone, and, correspondingly, several steps in the pathway have been postulated for these ketones. In general, the proposed pathways include an oxidative hydroxylation to the corresponding hydroxy ketone, followed by a reduction to the secondary alcohol or further oxidation to the dione. Although data do not exist for the other ketones, it is reasonable to suggest that they also follow these metabolic steps.

DiVincenzo et al [83] reported that male guinea pigs metabolized methyl n-butyl ketone, methyl isobutyl ketone, or methyl ethyl ketone, after a single ip dose of 450 mg/kg, to their corresponding alcohols, with subsequent oxidation steps occurring as shown in Table III-6. In general, all three ketones were both oxidatively and reductively metabolized. Oxidation occurred by hydroxylation of the omega-1 carbon, ie, the next to

the last carbon, to form the corresponding hydroxy ketone, and reduction occurred at the carbonyl group to form the corresponding secondary alcohol. Although the proportion of metabolites may differ, omega-1 oxidation and carbonyl reduction appear to be the initial steps in the metabolic pathways in guinea pigs.

TABLE III-6

METABOLISM OF SOME KETONES BY GUINEA PIGS

Ketone	Half-Life (min)	Clearance Time (hr)	Metabolites	Clearance Time (hr)
Methyl isobutyl ketone	66	6	4-hydroxy-4-methyl-2-pentanone	16
			4-methyl-2-pentanol	-
Methyl ethyl ketone	270	12	2-butanol	16
			5-hydroxy-2-butanone	16
			2,3-butanediol	16
Methyl n-butyl ketone	-	-	5-hydroxy-2-hexanone	-
			2,5-hexanedione	-
			2-hexanol	

Adapted from reference 83

DiVincenzo et al [83] concluded that the predominant metabolite of methyl n-butyl ketone was 2,5-hexanedione, which could be reduced to 5-hydroxy-2-hexanone but was probably not significantly converted to 2,5-hexanediol. Comparison of the metabolism of the hydroxy ketone and the dione showed that the formation of the dione was favored. Another metabolite, 2-hexanol, could be further metabolized to 2,5-hexanediol, 5-hydroxy-2-hexanone, 2,5-hexanedione, and to methyl n-butyl ketone. When n-

hexane was injected ip into guinea pigs at 250 mg/kg, 5-hydroxy-2-hexanone and 2,5-hexanedione were detected [83]. The authors noted the importance of finding 5-hydroxy-2-hexanone and 2,5-hexanedione as common metabolites of n-hexane and methyl n-butyl ketone because n-hexane also has been reported to cause peripheral neuropathy [84].

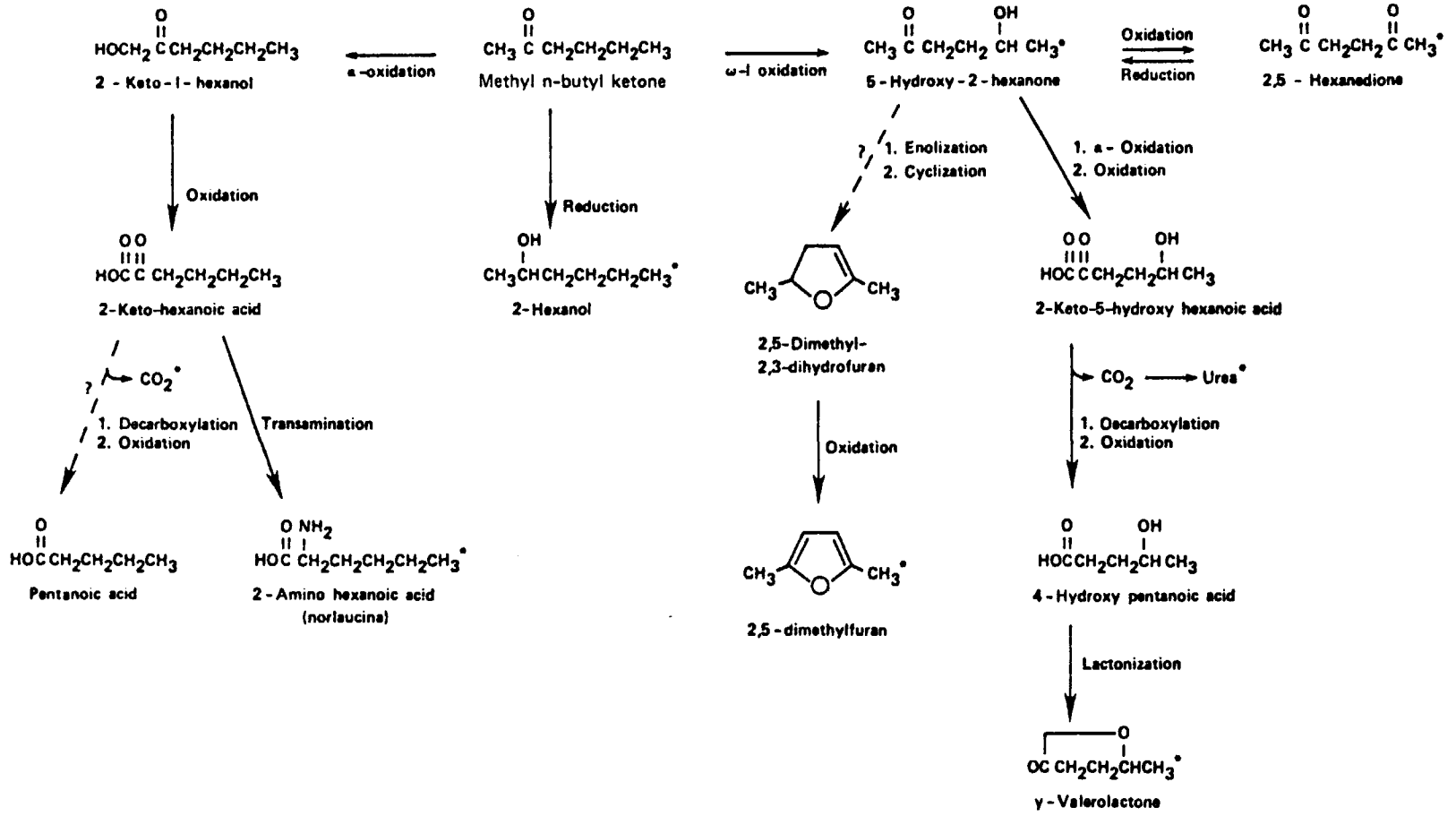
A later study by DiVincenzo and colleagues [85] in which 20 or 200 mg/kg of 14C-methyl n-butyl ketone was given by gavage to rats showed that about 6% of the administered dose was excreted in the breath as unchanged methyl n-butyl ketone and 38% as carbon dioxide. An additional 40% of the dose was excreted in the urine, and 8% remained in the carcass after 6 days. Serum metabolites were reported as 2-hexanol, 5-hydroxy-2-hexanone, and 2,5-hexanedione. Metabolites identified in urine were 2-hexanol, 5-hydroxy-2-hexanone, 2,5-hexanedione, 2,5-dimethylfuran, gamma-valerolactone, norleucine, and urea. Besides the reduction of the carbonyl group and oxidation of the omega-1 carbon atom, a major metabolic pathway was the oxidation of the alpha carbon to form an alpha-keto acid. Decarboxylation of this acid apparently accounted for most of the respiratory carbon dioxide produced. Transamination of the alpha-keto acid to form the amino acid, norleucine, was a minor metabolic pathway.

The authors [85] noted that pretreatment with SKF 525A produced an increase in respiratory carbon dioxide and a decrease in urinary radioactivity, suggesting that omega oxidation was mediated by a microsomal mixed-function oxidase system. Phenobarbital pretreatment increased the amount of labeled carbon dioxide in the first 4 hours but did not alter its subsequent output. A proposed metabolic pathway developed largely from information on guinea pigs is shown in Figure III-1.

Krasavage et al [86] studied the neurotoxic effects of several methyl n-butyl ketone metabolites and n-hexane in rats. Equimolar doses of 6.6 millimoles/kg were given by gavage to male Charles River rats 5 days/week for 90 days. Relative neurotoxicity was evaluated by comparing the time of onset of severe hindleg weakness. The compounds studied were methyl n-butyl ketone, n-hexane, 2,5-hexanedione, 2,5-hexanediol, 5 hydroxy-2-hexanone, and 2-hexanol.

Microscopic and clinical examination showed that each compound except n-hexane produced a typical giant axonal neuropathy and severe hindleg footdrop [86]. The relative order of the neurotoxicity of the hexacarbon compounds studied, in decreasing order, was 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-hexanediol, methyl n-butyl ketone, and 2-hexanol. No evidence of neuropathy was found in n-hexane-treated animals or in controls.

Couri et al [87] reported that aniline hydroxylase activity was significantly increased in liver microsomal preparations from rats exposed continuously or intermittently (7 hours/day) for 7 days to a combination of methyl ethyl ketone and methyl n-butyl ketone ($P<0.05$). The continuous exposure significantly increased aminopyrine demethylase, para-nitrobenzoate reductase, and neoprontosil reductase activities in the microsomal preparations ($P<0.01$). Intermittent exposure caused a significant decrease in para-nitrobenzoate reductase activity ($P<0.05$), but it did not affect aminopyrine demethylase or neoprontosil reductase activities. The explanation for the discrepancy in the data on the effect of ketone exposure on the activity of para-nitrobenzoate reductase is not apparent. However, it seems evident that methyl ethyl ketone can stimulate



* Designates compounds actually identified as metabolites.
From DiVincenzo et al [83]

FIGURE III–1

PROPOSED PATHWAY FOR THE METABOLISM OF [1-14 C] METHYL n-BUTYL KETONE

methyl n-butyl ketone metabolism and thus increase the production of 2,5-hexanedione which is neurotoxic [72].

In 1943, Treon et al [88] found a decrease in the ratio of inorganic sulfates to total sulfates and an increase in the level of glucuronic acid in the urine of rabbits exposed to cyclohexanone. On the basis of a monomolecular conjugation, the investigators determined that approximately 45-50% of the administered oral dose was excreted in conjugation with glucuronic acid. Elliott et al [89] also reported that rabbits given 248 mg/kg of cyclohexanone by stomach tube eliminated 66% (51-86%) of the administered dose as cyclohexylglucuronide in the urine. Because cyclohexanol also was metabolized to cyclohexylglucuronide, it is possible that cyclohexanone is first reduced to cyclohexanol and then is conjugated with glucuronic acid. James and Waring [90] showed that rabbits and rats given oral doses of cyclohexanone excreted trace amounts of hydroxycyclohexylmercapturic acid and cis-2-hydroxycyclohexylmercapturic acid in the urine. From these data [88-90], it seems reasonable to conclude that the principal metabolic pathway of cyclohexanone in rats and rabbits is reduction to cyclohexanol and subsequent conjugation with glucuronic acid.

Abdel-Rahman et al [91] found a peak blood methyl n-butyl ketone concentration of 650 μg/ml in male rats given a 160-mg ip dose of methyl n-butyl ketone. The half-life for the rapid elimination from the blood was about 10 minutes, followed by a slower phase of elimination with a 7-hour half-life. When male rats were continuously exposed to methyl n-butyl ketone at 400 ppm for either 6 or 60 days, the parent compound could not be detected in the blood.

Guinea pigs receiving phenobarbital prior to methyl n-butyl ketone ip injections had increased 2-hexanol concentrations in the blood at 100 minutes after exposure and substantially increased 2,5-hexanedione concentrations at 50, 100, and 180 minutes after exposure [91]. In rats, phenobarbital conditioning increased 2-hexanol concentrations 200 minutes after exposure and increased 2,5-hexanedione concentrations at 50, 100, 160, and 200 minutes after exposure. Phenobarbital also enhanced the urinary excretion of 2,5-hexanedione in rats and of methyl n-butyl ketone, 2-hexanol, and 2,5-hexanedione in guinea pigs.

In another experiment, 61% of a total ip dose of tritiated methyl n-butyl ketone administered to rats was recovered in 72 hours [91]. In the first 24 hours, 12.7% was excreted in the expired air, 31.8% in the urine, and 2% in the feces; in the first 72 hours, these values were 12.8, 40.1, and 7.9%, respectively.

Raleigh and coworkers [72] also reported that 2,5-hexanedione was a major metabolite of methyl n-butyl ketone in several species of animals. Peripheral neuropathy was produced in rats by a daily sc injection of an average of 340 mg/kg of 2,5-hexanedione, 5 days/week, for 19 weeks or by an average dose in drinking water of 520 mg/kg/day for about 2 months. Although many experimental details were omitted, these findings are in agreement with the results of other investigators [71,78,92].

(f) Carcinogenesis, Mutagenesis, Teratogenesis, and Effects on Reproduction

No studies implicating the ketones as possible carcinogens or mutagens were found in the literature. However, some studies that produced

negative results were found. McCann et al [93] found that acetone was not mutagenic in the Ames test. Van Duuren et al [94] applied 0.1 ml of acetone 3 times/week to the skin of mice for 1 year and found no evidence of tumors 208 days later. McLaughlin et al [95] injected 39 and 78 mg of acetone into the yolks of fertile chick eggs prior to incubation and found no evidence of teratogenicity. DiPaolo et al [96] used an acetone concentration of 0.02% or less in the growth medium of cultures of embryonic cells of the Syrian hamster uterus and found no transformation to altered clones of diminished cloning efficiency. NIOSH found no evidence of mutagenic activity in cyclohexanone by the Ames test (G Taylor, written communication, March 1978).

Schwetz et al [97] exposed pregnant Sprague-Dawley rats to methyl ethyl ketone in a study of possible teratogenic effects. On days 6-15 of gestation, 23 rats were exposed to methyl ethyl ketone for 7 hours/day at an average concentration of 1,126 ppm, and 21 rats were exposed at an average concentration of 2,618 ppm. A control group of 43 pregnant rats was exposed to filtered room air. Observations and measurements included maternal and fetal mortality, gross appearance and body weight, maternal liver weight and behavior, number of resorptions, and serum glutamic-pyruvic transaminase (SGPT) activity on day 21 of gestation.

No gross anomalies were observed in the dams exposed at either concentration [97]. Exposure to methyl ethyl ketone did not appreciably affect the number of corpora lutea/dam, the number of implantation sites/litter, the number of live fetuses/litter, or the percentage of resorptions. Methyl ethyl ketone at 1,126 ppm significantly reduced the fetal body weights and fetal crown to rump length ($P<0.05$), but these

changes were not apparent in rats exposed at the higher concentration. No gross anomalies were observed in the fetuses of rats exposed at 1,126 ppm, but four fetuses were affected at the higher concentration. Two of these had short lower jaws, and two had no tails with an imperforate anus. The authors stated that these anomalies had never been seen in over 400 control litters that had been examined in their laboratory. The total incidence of skeletal anomalies was significantly greater than the control incidence for the group exposed at 1,126 ppm but not in the rats exposed at 2,618 ppm. The most prevalent skeletal effects involved the sternum, and rats exposed at 2,618 ppm had a significantly greater number of sternal anomalies than did the controls. Total soft tissue effects, including subcutaneous edema and dilated ureters, were more frequent in the offspring of exposed rats than in the controls, but the difference was significant only at the higher concentration.

Exposure to methyl ethyl ketone did not affect maternal body weight, maternal liver weight, liver appearance, SGPT activity, or the general behavior of the rats [97].

Rats exposed at the higher concentration occasionally ate less food than did controls; while this difference was statistically significant during two 2-day measuring periods, the difference was only about 10-15%. The authors concluded that methyl ethyl ketone, on the basis of these results in fetuses from dams exposed to the solvent, was embryotoxic, fetotoxic, and potentially teratogenic to rats. It is difficult to draw conclusions from this study with confidence because of the lack of a dose-response relationship from such effects as total skeletal anomalies and fetal size, ie, crown to rump length. On the other hand, the greater

incidence of sternebral and soft tissue anomalies at the higher concentration lends some credence to the results. It is noted that the data were analyzed by litters rather than in terms of individual animals. An analysis of data on individual animals might also have been useful.

Because of the possible implications of this study in terms of hazards to unborn children of working mothers, it is important that this work be verified or refuted by additional research, both in terms of this specific ketone and in terms of other ketones.

Griggs et al [98] studied the effects of cyclohexanone on chick embryos. Fertile eggs were placed in a 37 C incubator containing cyclohexanone at an undescribed concentration. Two groups of eggs were exposed for 3 or 6 hours prior to incubation. Three other groups were similarly exposed for 3, 6, or 12 hours after being incubated for 96 hours. After exposure, eggs were kept in hatching incubators for 13 days, and then most embryos were examined for viability, gross appearance, and microscopic changes in the heart, liver, and brain [98]. In addition, blood serum tests, including determinations of serum cholesterol, bilirubin, albumin, uric acid, urea nitrogen, lactate dehydrogenase, lipids, alkaline phosphatase, calcium, inorganic phosphate, serum glutamic-oxaloacetic transaminase (SGOT), mean packed erythrocyte volume, and hemoglobin concentration, were performed on selected embryos.

The body weight of all exposed embryos without incubation before exposure were significantly less than those of their respective controls ($P<0.01$) [98]. In contrast, the weights of the exposed embryos that had 96 hours of incubation before exposure varied with respect to controls. The only changes in serum indices after exposure to cyclohexanone were a

decreased calcium level and an increased inorganic phosphate concentration and SGOT activity. Gross inspection of the chicks showed no effects on the head, beak, toes, eyes, and feathers. No changes were found in the hearts and brains that were examined, but livers of exposed chicks appeared darker than those of the controls.

Chicks that hatched from eggs exposed to cyclohexanone for 3 hours after a 96-hour incubation could not stand and exhibited spastic motions when they tried to move [98]. Their only anatomical abnormality was a curling inwards of their toes. No changes were noticed in the chicks that hatched from eggs exposed for 6 or 9 hours, but 20-50% of the exposed eggs did not hatch compared to 10-20% of the control eggs. The authors did not examine the nervous systems and therefore could not determine whether cyclohexanone acted centrally or caused lesions in the peripheral nervous system. Interpretation of the implications of these results should, if possible, await confirmation in placental mammals.

Correlation of Exposure and Effect

All of the ketones except methyl isoamyl ketone have been reported to cause some degree of systemic organ damage [20,21,34,54,57,99] which generally occurred only at very high concentrations. Some of the ketones, however, have produced significant organ damage at lower concentrations. Cyclohexanone at 608 ppm for 300 hours produced extensive injury to heart muscle, lungs, liver, and kidneys in monkeys [54]. Mesityl oxide at 250 ppm for 240 hours caused congestion in livers and lungs and dilated Bowman's capsules and swollen convoluted tubular epithelium in the kidneys

of guinea pigs [21]. Isophorone at 500 ppm for 240 hours produced severely injured kidneys or lungs or both in rats and guinea pigs.

All of the ketones except methyl isoamyl ketone have been reported to produce irritation of the eyes, nose, or throat. Specht et al [34] gave evidence suggesting that the irritation produced by the homologous ketones increased in proportion to the number of carbon atoms. Acetone, for example, was only slightly irritating at 20,000 ppm, but methyl n-butyl ketone was extremely irritating at 6,000 ppm. The nonhomologous six-carbon ketones (methyl isobutyl ketone, cyclohexanone, and mesityl oxide) were also extremely irritating. Specht et al [34] found that methyl n-butyl ketone and cyclohexanone at 6,000 and 4,000 ppm, respectively, produced clouding of the corneas of guinea pigs that persisted after the exposure period. Rengstorff et al [66] found that cutaneous application of 0.5 ml of acetone or cyclohexanone and sc administration of 0.05 ml of acetone or cyclohexanone, three times/week for 3 weeks, produced cataracts in guinea pigs. Generally, the cataracts were first seen 3 months after treatment with the ketones. In some cases, lens damage was reversed within the first 3 months.

The results of sensory threshold studies in humans [15,16] also indicate that the high molecular-weight ketones are, in general, more irritating. Isophorone, a ketone that contains nine carbon atoms, was perceived as being irritating by the subjects at significantly lower concentrations than those of acetone and methyl ethyl ketone that caused irritation [15]. Yant et al [52] reported that methyl n-propyl ketone at 1,500 ppm produced moderate to marked irritation of the eyes and nose of humans after an unspecified exposure period. Raleigh and McGee [17] found

eye, nose, and throat irritation in a small group of workers exposed to acetone for 8 hours at an average concentration of 1,000 ppm. Matsushita et al [18] reported that most subjects exposed to acetone at 500 and 1,000 ppm had irritation of the eyes, nose, and throat.

Probably because of their excellent lipid solvent properties and, thus, their defatting action, the liquid ketones produce adverse effects on the skin. Lupulescu and Birmingham [32] found intercellular edema and disruption of the cells of the keratin layer in volunteers exposed to liquid acetone. Smith and Mayers [33] reported that methyl ethyl ketone at 300-600 ppm produced dermatitis in exposed workers after an unspecified period of exposure. Linari et al [30] found skin lesions in 3 of 19 workers exposed to methyl isobutyl ketone at 80-500 ppm for 20-30 minutes daily. These lesions were described as varying from erythema to small desquamative areas after an initial dry dermatitis. In a follow-up study, Armeli et al [31] reported that dermal lesions were markedly reduced. At that time, workers were required to wear gloves and barrier creams. The workplace environment contained methyl isobutyl ketone at 50-105 ppm, and exposures lasted for 15-30 minutes daily. These findings and the ability of ketones to dissolve lipids suggest that ketones in liquid form may cause dermatitis. The question of whether ketone vapor can cause dermatitis is not settled, but it seems unlikely; except for some exposures to methyl ethyl ketone vapor that appeared to be responsible for dermatitis of the face [33], liquid contact was the more likely cause.

Smyth et al [61,62] studied the primary skin irritation produced by ketones on rabbits. Methyl n-amyl ketone produced the most severe irritation of the ketones considered in this document and was assigned a

grade of 4. (Grade 6 compounds produced necrosis when applied undiluted.) Methyl ethyl ketone was grade 2, and acetone, methyl n-propyl ketone, and methyl n-butyl ketone were grade 1, indicating minimal visible capillary injection.

Little information was available on percutaneous absorption, although the more lipid-soluble ketones would be expected to penetrate the skin more readily than the less lipid-soluble ketones. In this respect, Cesaro and Pinerolo [24] demonstrated that acetone concentrations in the blood were not increased after nude volunteers were exposed to acetone vapor at unspecified concentrations for 20-30 minutes. However, Parmeggiani and Sassi [27] showed that acetone was absorbed percutaneously when applied to the skin of a subject for 30 minutes and the subject remained in a chamber for an additional 1.5 hours. This was demonstrated by the levels of acetone found in the blood and urine. Munies and Wurster [43] showed that methyl ethyl ketone was excreted in the expired air in a few minutes after the ketone was placed on the forearm of volunteers. Billmaier et al [38] suggested that skin absorption was probably a contributing factor in the development of peripheral neuropathy in the workers exposed to methyl n-butyl ketone in a coated-fabric plant. Studies by DiVincenzo and colleagues [45] support this theory. They demonstrated that methyl n-butyl ketone was absorbed through the skin of volunteers at the rate of 4.2-8.0 μg/minute/sq cm.

All of these ketones except methyl isoamyl ketone have been reported to cause narcosis or signs of CNS depression. However, had this compound been studied, it seems likely that it, like the related ketones, would also have been found to have caused CNS depression. Acute intoxication of a 10-

year-old boy with acetone resulted in collapse, stupor, and incoherence [23]. Eight workers exposed to acetone at a concentration greater than 12,000 ppm felt dizzy and lightheaded and reported weakness of the legs [25]. Raleigh and McGee [17] noted headache and lightheadedness in workers exposed to acetone for 8 hours at an average concentration of 1,000 ppm. Parmeggiani and Sassi [27] found irritation of the eyes, nose, throat, and lungs and CNS disturbances in workers exposed to acetone at 307-918 ppm. The authors attributed these effects to slight accumulations of acetone in the body resulting from repeated exposure to the compound. Vigliani and Zurlo [28] reported occasional dizziness and loss of strength in workers exposed to acetone at 1,000 ppm 3 hours/day for 7-15 years. DiVincenzo et al [42] exposed nine volunteers to acetone at 100 or 500 ppm for 8 hours with no symptoms reported except for an awareness of acetone at 500 ppm. He also presented evidence that acetone might accumulate in the body at these concentrations.

GD Ware (written communication, June 1973) reported to the ACGIH that isophorone at 5-8 ppm caused fatigue and malaise in workers. When concentrations were reduced to 1-4 ppm, no adverse effects were reported.

In animals, Specht et al [34] reported narcosis and decreased rectal temperature, respiratory rate, and pulse rate in guinea pigs exposed to acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, methyl n-amyl ketone, methyl isobutyl ketone, mesityl oxide, or cyclohexanone. Exposures lasted from 204 to 1,405 minutes. Their findings, as summarized in Table III-4, indicated that in general the high molecular weight ketones were stronger narcotic agents than the low molecular weight ketones. Carpenter et al [20] reported that male rats

exposed to diisobutyl ketone for 7 hours at 1,650 ppm were prostrate at the end of the 1st day and had poor coordination at the end of the 2nd day. Lehmann and Flury [57] found that diacetone alcohol caused exhaustion in rats, mild narcosis in rabbits, and sleepiness in mice, rabbits, and cats. Smyth and Seaton [58] noted that single exposures to isophorone produced narcosis in rats and guinea pigs.

It is well established that the ketones can produce narcosis at high concentrations, so it seems reasonable to infer that modification of behavior or impairment of judgment could also occur. Exposure to acetone at concentrations that were less than those causing unconsciousness in humans did produce stupor, dizziness, and lightheadness, as might be expected [17,23,25]. Such effects could lead to serious consequences in the workplace. Goldberg et al [79] found that, in rats, acetone at concentrations of 6,000 ppm produced modification of behavior involving avoidance and escape patterns. Johnson and colleagues [80] demonstrated that the response rate in operant behavioral performance was decreased in rats that were exposed to methyl n-butyl ketone at 976 ppm for 6 hours/day, 5 days/week, after 2 weeks of exposure. Anger and coworkers [81] studied rats trained on a multiple fixed-ratio, fixed-internal (FRFI) schedule of reinforcement. They found methyl n-amyl ketone at 175 mg/kg ip produced a near cessation in the fixed interval response rates. Similar effects that were not statistically significant were found in rats exposed at 1,600 ppm.

Peripheral neuropathy is the most serious occupational illness related to exposure to these ketones. Exposure to methyl n-butyl ketone has been associated with this neurologic disorder [37,38,47].

Allen et al [37] reported that 11 workers in a coated-fabric plant

had a characteristic disabling peripheral neuropathy that was described as a distal, motor, and sensory disorder with an insidious onset and minimal reflex loss. Electromyographic abnormalities were approximately symmetrical and were either restricted to a distal distribution or greater in degree in distal muscles than proximal ones. Some of the affected workers had washed their hands with a solvent that contained methyl n-butyl ketone, although employees who operated the printing machines had ample opportunity to inhale the solvent vapors. Analysis of the area around the print machines showed methyl ethyl ketone at 331-516 ppm and methyl n-butyl ketone at 9.2-36 ppm. Other investigators [39,41] have found similar signs of neurologic disorders in workers exposed to methyl n-butyl ketone. These studies also indicated that skin contact with methyl n-butyl ketone contributed to the development of the peripheral neuropathy.

The incidence of peripheral neuropathy in the print department of the coated-fabric plant was 21.5%, which was highly significant ($P<0.001$) when compared to other departments [37,47]. Area atmospheric samples showed that printers were exposed to methyl n-butyl ketone at calculated TWA concentrations ranging from 2 to 50 ppm. However, because of the poor work practices at the coated-fabric plant, it was not certain whether the outbreak of peripheral neuropathy was caused by inhalation or skin absorption of methyl n-butyl ketone or by a combination of both routes of exposure. Questionnaire results showed that workers washed their hands with the solvent containing methyl n-butyl ketone, cleaned machines with rags dipped by hand in open containers of the solvent, and washed their work clothes with the solvent at the plant. Since methyl n-butyl ketone penetrates human skin [45], it is highly probable that skin absorption, as

a result of the aforementioned poor work practices, played a significant part in the development of peripheral neuropathy in this case.

DiVincenzo et al [45] have shown that about 75-92% of inhaled methyl n-butyl ketone was absorbed by volunteers. When applied to the skin of volunteers, about 5 μg/minute/sq cm was absorbed. From these data, it can be calculated that immersion of both hands in liquid methyl n-butyl ketone for 15 minutes results in the absorption of approximately 13% of the amount of ketone absorbed by a worker who is exposed to airborne methyl n-butyl ketone at the average TWA concentration of 13.1 ppm. If the immersion time had been as much as 30 minutes/day, the contribution of percutaneous ketone would have been about one fourth. There is no good information on the role of ingestion in these intoxications, but it is thought to have been minor or perhaps even negligible.

Several studies on animals have confirmed that methyl n-butyl ketone causes peripheral neuropathy [70,71,74,76,77,80,91]. Mendell et al [70] reported peripheral neuropathy in chickens, rats, and cats exposed to methyl n-butyl ketone at 200-600 ppm for 24 hours/day, 7 days/week. Krasavage et al [76] found that methyl n-butyl ketone vapor at 330 ppm, but not at 100 ppm, caused clinical and microscopic evidence of neuropathy in rats. DeJesus and coworkers [77] found no evidence of neuropathy in rats exposed to methyl n-butyl ketone vapor at 60 and 90 ppm. In contrast, Johnson et al [80] reported that decreased motor conduction velocities occurred in monkeys exposed at 97 ppm for 9 months.

Although most of the available evidence indicates that, of these ketones, only methyl n-butyl ketone can cause peripheral neuropathy, studies implicating other ketones have been found [33,36,71]. Viader et al

[36] found evidence of peripheral neuropathy in a man who worked with an adhesive composed of 60% tetrahydrofuran and 40% of a polyester-type polymer. The man also worked with a solvent that was reported to be 100% methyl ethyl ketone. Viader postulated that the man's illness was caused by exposure to methyl ethyl ketone or by a combined exposure. Smith and Mayers [33] reported that workers exposed to methyl ethyl ketone at concentrations ranging from 300-600 ppm developed numbness of the fingers and arms. One worker complained of numbness in the legs. Spencer et al [71] found minimal neuropathic changes in rats exposed to methyl isobutyl ketone, but they attributed this to the presence of methyl n-butyl ketone as a contaminant, a reasonable conclusion in the light of their later study [74] showing that methyl isobutyl ketone of greater than 98.8% purity caused no neurotoxic effects.

In animals, several studies [73,74,77] have shown that methyl ethyl ketone alone did not produce neurotoxicity. However, methyl ethyl ketone did shorten the latency period for the onset of neurotoxic effects of methyl n-butyl ketone in cats. The reason for this effect is not understood. Couri et al [87] reported results that indicated that methyl ethyl ketone might have stimulated the metabolism of methyl n-butyl ketone, which might explain the enhancement of toxicity. Saida et al [73] found no evidence of neuropathy in rats exposed continuously to methyl ethyl ketone at 1,125 ppm for about 7 months. Spencer and Schaumburg [74] found no neuropathy in rats injected sc twice daily with 150 mg/kg for 5 days/week for 8.5 months. DeJesus et al [77] were unable to demonstrate any neuropathy in rats exposed to methyl ethyl ketone at 2,150 ppm for 6 weeks or at 4,740 ppm for 4 weeks.

Johnson et al [82] exposed rats and monkeys to methyl n-amyl ketone at 131 and 1,025 ppm for 6 hours/day, 5 days/week for 9 months and found no evidence of neuropathy. This finding is particularly significant because methyl n-amyl ketone is one of the two closest homologs of methyl n-butyl ketone.

DiVincenzo et al [83] demonstrated that in guinea pigs methyl ethyl ketone, methyl n-butyl ketone, and methyl isobutyl ketone were metabolized by omega-1 oxidation to form the corresponding hydroxy ketone, and by carbonyl reduction to form the corresponding secondary alcohol. The hydroxy ketone underwent further transformation to the diol by reduction or to the dione by oxidation. They noted that 2,5-hexanedione and 5-hydroxy-2-hexanone were also metabolites of n-hexane, which has been shown to cause peripheral neuropathy.

Krasavage et al [86] found in a study with rats that the relative order of neurotoxicity for methyl n-butyl ketone and its metabolites was 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5 hexanediol, methyl n-butyl ketone, and 2-hexanol. n-Hexane was not neurotoxic under the conditions of this experiment.

Saida et al [73] have shown that methyl ethyl ketone increased the toxicity of methyl n-butyl ketone, whereas methyl ethyl ketone alone at 1,125 ppm was not neurotoxic in cats [73,74]. Rats continuously exposed to methyl n-butyl ketone at 225 ppm developed paralysis in 66 days. Animals exposed to a combination of methyl n-butyl ketone at 225 ppm and methyl ethyl ketone at 1,125 ppm developed paralysis after 25 days of exposure.

Spencer and Schaumburg [92] have shown that 2,5-hexanedione (previously shown by other investigators [83,91] to be a metabolite of

methyl n-butyl ketone) produced a pattern and distribution of peripheral and CNS degeneration similar to that produced by methyl n-butyl ketone itself. They suggested that the CNS degeneration might not be reversible [78]. However, Abdel-Rahman et al [91] found that phenobarbital pretreatment protected against the neurotoxic effects of methyl n-butyl ketone. They suggested that protection might have resulted from an increased rate of excretion of 2,5-hexanedione.

In a later study, DiVincenzo and colleagues [85] demonstrated that respiratory carbon dioxide was the major excretory product of methyl n-butyl ketone.

The vapor pressure and thus the volatility of the homologous ketones is inversely proportional to the number of carbon atoms (see Tables XI-1 and XI-2). Therefore, although the higher ketones are more toxic, exposure by inhalation would tend to be less as the number of carbons increases, thus reducing the relative hazard of the ketones. Because lipid solubility is directly proportional to the number of carbon atoms, the hazard associated with skin absorption would be expected to be greater with the higher ketones because the affinity of the higher ketones for dermal lipids would increase. These factors are important considerations in developing a hygiene program for the ketones.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports that implicated ketones as carcinogens or mutagens were found; some negative results were found for acetone [93-96] and for cyclohexanone (G Taylor, written communication, March 1978).

Schwetz et al [97] exposed pregnant rats to methyl ethyl ketone vapor and found some evidence of teratogenicity; however, because of the lack of a dose-response relationship in some of the effects, this evidence of teratogenicity should not be extrapolated to human effects until the effects on rats are confirmed or clarified. Griggs et al [98] demonstrated that embryos exposed to cyclohexanone produced chicks that could not stand and that exhibited spastic motions. In the absence of such information as data on placental transfer of ketones or their metabolites, whether these data from nonplacental embryos apply to human embryonic development is not evident.

Summary Tables of Exposure and Effect

Tables of selected effects of the ketones are presented below. Tables III-7 and III-8 show the irritative and systemic effects of the ketones, respectively, on humans. Table III-9 summarizes effects of the ketones on animals. Lastly, the effects on animals from inhaling methyl n-butyl ketone are given in Table III-10.

TABLE III-7

IRRITATION PRODUCED BY SOME KETONES IN HUMANS*

Ketone	Concentration/Duration	Effects	Reference
Acetone	800-1,000 ppm/8 hr	Slight-moderate eye irritation	17
"	500 ppm/6 hr	Irritation to eyes, nose, throat, and trachea	18
"	500 ppm/2-4 hr	No symptoms	42
Methyl ethyl ketone	33,000 ppm/momentary	Intolerable eye and nose irritation	19
"	3,300 ppm/momentary	Moderate eye and nose irritation	19
Diisobutyl ketone	100 ppm/3 hr	Slight eye and throat irritation, slight headache	20
"	50 ppm/3 hr	Slight transitory eye and nose irritation	20

*See also Table III-1

TABLE III-8

SYSTEMIC EFFECTS OF KETONES ON HUMANS

Ketone	Concentration/Duration	Effects	Reference
Acetone	Unknown	Vomiting, narcosis	23
"	Greater than 12,000 ppm/?	Throat and eye irritation, dizziness, weakness	25
"	Greater than 12,000 ppm/2 min	Dizziness and weakness	25
"	1000 ppm/3 hr/d, 7-15 yr	Inflammation of respiratory tract, stomach, duodenum; occasional dizziness, loss of strength	28
Acetone and Methyl ethyl ketone	330-495 ppm/? 398-561 ppm/?	Eye irritations, gastrointestinal disturbances, headache, and narcosis	33
Methyl ethyl ketone (possibly methanol)	Unknown	Retrobulbar neuritis	35
Methyl ethyl ketone	300-600 ppm	Dermatitis of the face, numbness of fingers and legs	33
Methyl ethyl ketone and tetrahydrofuran	Unknown	Peripheral neuropathy	36
Methyl n-butyl ketone and methyl ethyl ketone	6.1-36.0 ppm 147-516 ppm	"	37,38 47
Methyl n-butyl ketone	Unknown	"	39,41
Methyl isobutyl ketone	80-500 ppm/20-30 min/d	Weakness, loss of appetite, headache, eye irritation, stomach ache, nausea, vomiting, and sore throat	30
"	50-105 ppm/15-30 min/d	CNS and gastrointestinal disturbances in a few workers	31

TABLE III-9

EFFECTS OF KETONES ON ANIMALS[a]

Ketone	Concentration/Duration	Animal	Effects	Reference
Acetone	0.5 ml on the skin, 0.05 ml sc/3 times/wk, 3 wk	Guinea pigs	Cataracts	66
Methyl ethyl ketone	33,000-100,000 ppm/200 min	"	Gasping death, emphysema, slight congestion of brain, marked congestion of systemic organs especially the lungs, and corneal opacities	19
"	3,300 ppm/810 min	"	No abnormal signs	19
"	1,125 ppm/24 hr/3, 55 d	Rats	No evidence of peripheral neuropathy	74
"	1,126 or 2,618 ppm/7 hr/d on d 6-15 of gestation	Pregnant rats	Embryotoxicity, fetotoxicity and possible teratogenicity	98
Methyl n-propyl ketone	50,000 ppm/50 min	Guinea pigs	Death, slight congestion of brain and marked congestion of systemic organs	52
"	1,500 ppm/810 min	"	No abnormal signs	52
Methyl n-amyl ketone	1,025 ppm/6 hr/d for 2 wk	Rats and monkeys	No evidence of peripheral neuropathy	82
Methyl isobutyl ketone	200 ppm/24 hr/d for 2 wk	Mice, rats, dogs, and monkeys	Heavier liver and kidneys in rats	53
"	100 ppm/24 hr/d for 2 wk	"	Heavier kidneys in rats	53
"	100 ppm at 258 mm Hg/24 hr/d 90 d	Monkeys, dogs, rats	Inflammation of kidneys in 1 monkey, hyaline droplet degeneration of proximal tubules in all rats, normal clinical and hematologic measurements	53
"	150 mg/kg/twice/d, 5 d/wk 8.5 mo	Cats	No evidence of peripheral neuropathy	74
Diisobutyl ketone	1,650 ppm/7/hr/d, 5 d/wk for 6 wk	Rats	Higher kidney and liver weights, death, no microscopic changes except cloudy swelling of the liver and moderate lung congestion	20
Cyclohexanone	608 ppm/300 hr	Monkey	Extensive injury to heart muscle, lungs, liver, and kidneys	54
"	190 ppm/300 hr	Rabbits	Slight degenerative changes in liver and kidneys	54
"	0.5 ml on the skin, 0.05 ml sc/3 times/wk, 3 wk	Guinea pigs	Cataracts	66
"	Unknown/3-12 hr	Chick eggs	Embryotoxic	98
Mesityl oxide	13,000 ppm/30 min/d 6 d	Mice	Necrotic spots in liver, lung hemorrhage, alimentary tract distension, and death	55
"	250 ppm/8/hr/d, 5/d/wk 6 wk	Guinea pigs and rats	Congested livers and lungs, dilatated Bowman's capsules and swollen convoluted tubular epithelium	21
Isophorone	500 ppm/8 hr/d, 5 d/wk 6 wk	"	Severely injured kidneys and/or lungs, and death	21

[a]All of the ketones produced some irritation and narcosis.

TABLE III-10

EFFECTS ON ANIMALS EXPOSED
TO METHYL n-BUTYL KETONE BY INHALATION

Species	Concentration (ppm)	Duration	Observed Effects	Reference
Rats	1,300-2,000*	3-4 wk	Hindlimb footdrop	71
"	1,050*	5 wk	Peripheral neuropathy	77
Rats and monkeys	976*	25 wk	Hindlimb dragging	80
Rats	400 - 600**	5-8 wk	"	70
"	400**	42 d	Paralysis	73
"	330*	30 wk	Peripheral neuropathy	3
"	225**	66 d	Paralysis	73
"	100*	72 wk	No evidence of neuropathy	76
"	100*	4 wk	"	77
"	60*	6 wk	"	77
Cats	400 - 600**	11-12 wk	Limb dragging	70
"	330*	4.5 wk	Minimal microscopic changes	72
"	100*	4.5 mo	No evidence of neuropathy	72
Chickens	100 - 200**	4-5 wk	Unable to stand	70
Monkeys	97*	9 mo	Decreased motor conduction velocity	80

*6 hr/d, 5 d/wk
**Continuous

IV. ENVIRONMENTAL DATA

Sampling

A variety of common methods have been used over the years to sample airborne ketones in the workplace. These have included the use of impingers, bubblers, gas bags, and silica gel tubes. Currently, most ketone collection is done with charcoal tubes.

Impingers or bubblers containing absorbing liquids were the most common early methods used to collect ketone vapor. Smith and Wood [100] determined that a single absorber with water as the absorbent was 70 to 100% efficient in collecting acetone, methyl ethyl ketone, methyl isobutyl ketone, diacetone alcohol, mesityl oxide, and cyclohexanone in small air samples (125-1,625 ml). Kacy and Cope [101] recommended a fritted-glass bubbler for collecting airborne isophorone. Glacial acetic acid was the absorbent, and a sampling rate of 1 liter/minute for 5 minutes was used. No data on collection efficiency were presented. Andrew and Wood [102] used water as an absorbent in an impinger for isophorone sampling. Smith and Wood [99] used sodium nitroprusside and ammonium acetate in a bubbler to absorb acetone. A color complex was formed on the addition of ammonium solution, and the concentration was determined rapidly by visual comparison with standards. No efficiency data were presented. Acetone has also been collected in a series of two fritted bubblers with water as the absorbent [103].

Ketones have also been collected by the grab sample method using gas bags [104] or sample or prescription bottles [104,105]. Van Houten and Lee [105] found that the recovery of methyl isobutyl ketone was 95% after 30

days of storage in sample bottles and was 94% when samples were subjected to one week's storage over a temperature range of 0-175 F. The 1-week storage was used to simulate shipment by aircraft. Maykoski and Jacks [104] found recoveries of 91, 84, and 91% for collection of methyl ethyl ketone with a Scotchpac bag, Tedlar bag, and prescription bottle, respectively.

Using impingers, bubblers, and grab sample methods can be efficient ways to collect ketones, but such methods are undesirable for personal monitoring. Grab samples generally limit sample size; therefore, collection time is short. Impingers, bubblers, and other collection devices containing liquids may hamper the free movement of the worker. Spillproof impingers are commercially available, but these still have the problem of absorbent losses through evaporation and interference with movement.

More recently, solid sorbents in tubes, including silica gel, activated charcoal, and some chromatographic column packings have been used to collect ketones. The advantages of collection with a solid sorbent include the ability to collect samples over a wide range of sampling times, ease of transportation over that of air bags and impingers, minimal restriction on workers' movements, and collection efficiency. Some disadvantages are loss of the sample if the concentration of the ketone exceeds the adsorption capacity of the sorbent, the decrease in adsorption capacity with increasing humidity, and the need to determine or predict desorption efficiency.

Erley [106] reported 100% recovery of acetone from silica gel using thermal desorption at 400 C. A sampling rate of 1-3 liters/minute was

used. Buchwald [107] has stated that acetone can be removed from silica gel by desorbing with 1 N sodium hydroxide. In a review, Buchwald [108] recommended 20/40 mesh silica gel and stated, without providing data, that variations in humidity did not interfere with the sampling. Feldstein et al [109] used silica gel to collect methyl ethyl ketone and methyl isobutyl ketone.

In 1976, Parkes et al [110] reported results showing 96-99% primary tube collection efficiency on preconditioned 80/100 mesh Chromosorb 101 for a variety of ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl n-amyl ketone, and cyclohexanone when they were removed from the sorbent by thermal desorption.

Activated charcoal is the most widely used and tested of the solid sorbents. Fraust and Hermann [111] determined that 0.7 g of 10/30 mesh charcoal and a sampling rate of 100-200 ml/minute were most efficient for sampling methyl ethyl ketone. The volume of air sampled did not affect efficiency except in the case of methyl ethyl ketone, but efficiency decreased as the contaminant concentration in the air increased. Charcoal tubes also have good storage characteristics when stored at or below room temperatures. Sadenwasser [112] found no loss of acetone (472 ppm) or methyl ethyl ketone (189 ppm) when the substances were stored for 6 days on a 2-inch section of 10/20 mesh charcoal. When White et al [113] used a 1-inch section of charcoal for collection and carbon disulfide for desorption, methyl ethyl ketone recoveries were over 90%, even when 13 other solvents were simultaneously collected.

NIOSH has investigated and validated charcoal tube sampling for many ketones [114,115]. Experimental results on breakthrough for these ketones

are presented in Table IX-2. These data show that the efficiency of charcoal tube collection is adequate at the recommended concentration limits. For the selected ketones in this document, breakthrough from overloading the charcoal should not be a problem except at unusually high ketone concentrations, and it can be avoided by decreasing the sample volume.

Charcoal tube collection has many advantages. The tubes are inexpensive and readily available. They do not interfere with the workers' movements, and methods including charcoal tube collection have been validated; however, the sample volume is limited by the amount of the ketone which can be adsorbed on a given amount of charcoal, and there is the possibility of breakthrough. For these reasons, charcoal sampling is recommended for these ketones; details of the recommended sampling method are given in Appendix I. The presence of ketone aerosols does not seem likely because of the volatility of these substances. However, should such aerosol formation occur, it will probably be sorbed on charcoal if the airborne concentration is not too high. If any such aerosols are formed, possible breakthrough should be investigated.

The pump used to pull air through the collecting device should be a personal sampling pump capable of maintaining a constant flowrate of about 0.2 liters/minute (within 5%) across the pressure drop of the charcoal tube. Because the ketones exhibit various degrees of flammability, only pumps that are certified explosion-proof should be used, especially where the concentrations of airborne ketones are suspected or known to be high.

The recommended sampling method, as well as other methods discussed above, does not allow for continuous 10-hour sampling. Therefore, several

samples may be required to accurately determine the TWA exposure of any given employee. For a discussion of the estimation and calculation of TWA exposure concentrations from less than full-shift samples, refer to the NIOSH report, Occupational Exposure Sampling Strategy Manual [116].

Analysis

There are many methods available for the analysis of ketones in environmental samples. Colorimetry using detector tubes, gas-liquid chromatography, titration of iodoform, and ultraviolet absorption spectroscopy are the most common analytical methods.

Methyl ketones have been analyzed for many years by the iodoform test [103,117,118]. In this test, iodine in the presence of a base, which is often the sampling medium, reacts with the methyl group of the ketone to yield iodoform. Excess iodine is determined by titration with an indicator, such as thiosulfate, and the concentration of ketone is then calculated. This method can be used to measure ketones at low concentrations. For example, acetone can be measured at a concentration of 10 ppm in a 1-cu ft air sample, approximately 23.7 mg/cu m, [103], and 1 mg of mesityl oxide [119] and 0.73 mg of methyl ethyl ketone [120] can be measured in a 25-liter sample. However, any compound that reacts with iodine to form iodoform, eg, many alcohols, aldehydes, and other ketones, will interfere.

The formation of colored complexes has also been used to analyze ketones. In a field test method, Smith and Wood [100] collected acetone, methyl ethyl ketone, methyl iso-butyl ketone, diacetone alcohol, and mesityl oxide in water and reacted them with 2,4-dinitrophenylhydrazine.

When potassium hydroxide in methanol was added, a red color developed, which was compared visually to standards, allowing a rough determination to the nearest 500 ppm. Haidle and Knight [121] reported that methyl n-amyl ketone could be measured by the 2,4-dinitrophenylhydrazine method over the range of 0.25-3.0 μmol when a spectrophotometer was used rather than visual comparison to standards. Isophorone has been measured colorimetrically by its reaction with phosphomolybdic acid in glacial acetic acid. Over the range of 12-93 μg, isophorone was measured with a standard deviation of 40 μg. Andrew and Wood [102] used dodecamolybdophosphoric acid with perchloric acid to analyze isophorone in a range-finding field test method. Concentrations were determined to the nearest 35 mg/cu m over the range of 0-140 mg/cu m. When they are performed carefully, most colorimetric methods can provide accurate and precise results. Field test methods are also available for range-finding purposes. However, these rapid methods tend to be inaccurate. Accurate results are time consuming, and quick tests are usually not accurate [100,102].

Ultraviolet spectrophotometry has also been used to measure ketones. Isophorone in isopropanol absorbs ultraviolet light at 235 nm, and concentrations down to about 14 μg of isophorone can be detected in a 25-liter air sample by this method [122]. Acetone concentrations of about 4.5 mg in a 25-liter sample can also be measured [103]. Interference can occur whenever two or more compounds are present, including aromatic and unsaturated compounds that absorb ultraviolet light at similar wavelengths.

Direct reading instrumentation is available for real time and continuous monitoring of the ketones. Infrared spectrophotometers, equipped with adjustable, long pathlength gas cells, can be used and

provide quick, accurate measurement of the workplace concentrations. Analytical wavelengths of 8.2 μm (acetone), 8.3 μm (cyclohexanone), 8.5 μm (methyl ethyl ketone, methyl isobutyl ketone, and diacetone alcohol), and 8.6 μm (methyl isoamyl ketone, diisobutyl ketone, methyl n-butyl ketone, and methyl n-amyl ketone) have been used and have a minimum detectable concentration with a 20-meter cell of less than 1 ppm for each ketone [123]. The ketone wavelengths overlap and, therefore, where more than one ketone is present, the result may indicate the total amount present without allowing for separate determinations for each ketone. Combustible-gas meters and hydrocarbon meters are also available and, although nonspecific, can be useful for leak determinations.

Detector tubes or indicator tubes are being used more frequently since personnel require little specialized training to use them; they are inexpensive; and they give rapid estimations of exposure concentration. Indicator tubes are available for acetone (Draeger 100B, MSA 460423, and Kitagawa 102A) and methyl ethyl ketone (Kitagawa 139 B) according to a study of a working group of the British Occupational Hygiene Society [124]. Only the MSA acetone tube had been certified by NIOSH as of June 1976. The certified range of use was 500-5,000 ppm.

Gas-liquid chromatography (GLC) is widely applicable to the analysis of ketones. NIOSH has validated a GLC method for 11 of the 12 ketones, and the 12th, methyl isoamyl ketone, should be readily adaptable to this method [114,115]. In April 1977, documentation of the various validation tests of many of the methods was published by NIOSH [125]. Other investigators have also tested GLC methods for many of the ketones. McDonald et al [126] noted a retention time for acetone with a Porapak Q column of 0.88 minute

and 0.65 minute relative to n-propanol. Cooper et al [127] were able to detect as little as 2.6 μg of methyl ethyl ketone in a 10-liter air sample when the GLC method was used with a mass spectrophotometric detector. The limits of detection achievable with a mass spectrophotometer are not necessary for routine industrial hygiene monitoring; sufficient results are attainable with a flame-ionization detector. White et al [113] reported measuring methyl ethyl ketone by means of GLC analysis in the presence of 13 other solvents.

For these reasons, GLC is recommended for quantitation of these ketones; details of the analysis and a general method applicable to all 12 ketones are given in Appendix I. Methods for many of the individual ketones have been published in the latest edition of the NIOSH Manual of Analytical Methods [114,115]. The GLC operating conditions, validated ranges, coefficients of variation, and standard deviations have been determined and are listed in Tables IX-1 and IX-3.

An important step in the use of GLC for ketone analysis is the desorption of the compound(s) from the solid sorbent used to collect the ketones from the sampled air. Charcoal or silica gel tubes are the most commonly used collection methods, and the validated charcoal tube procedure has been recommended as described in Appendix I. Feldstein et al [109] used dimethyl sulfoxide, carbon disulfide, and a carbon disulfide-water mixture as a solvent to desorb methyl ethyl ketone or methyl isobutyl ketone from silica gel. Carbon disulfide and the carbon disulfide-water mixture gave unacceptable recoveries of 4-75%; dimethyl sulfoxide desorption was 97-98% efficient. NIOSH [114,115,125] has tested and validated the use of carbon disulfide as the desorbing solvent for use with

ketones collected on charcoal tubes. Regardless of the solid sorbent and desorbing solvent used, it is necessary to determine the desorption efficiency for each batch of analyses. Directions for this determination are included in Appendix I.

Environmental Data

Data on current and past occupational exposures to the ketones in this document are found only infrequently. Acetone and methyl ethyl ketone have been the most frequently monitored ketones.

Many NIOSH reports of health hazard evaluations [128-136] contain data on exposures to ketones in many different industries, but sampling of airborne ketones was performed primarily where the ketones have been used as solvents. The NIOSH method validated for the particular compound was used to obtain the data. Data from many such reports are briefly summarized in Table IV-1.

Data on methyl n-butyl ketone exposures during its manufacture have been reported to NIOSH [145]. Monitoring was performed during the summer of 1977. Operator breathing zone samples, collected during process sampling and laboratory analysis, averaged 41 mg/cu m with a range of from less than 0.01 up to 746 mg/cu m for 28 samples. Three samples taken in the operators' breathing zone during rail tank car loading were reported as containing a high of 187 mg/cu m and a low of 8 mg/cu m. Six samples taken during drum loading had methyl n-butyl ketone concentrations ranging from less than 4 to 27 mg/cu m.

Results from recent (April 1977) monitoring at the coated-fabric plant in Ohio have shown a reduction in environmental concentrations of

TABLE IV-1

ENVIRONMENTAL DATA FROM HEALTH HAZARD EVALUATION REPORTS

Compound	Use or Operation	Concentrations Mean (mg/cu m)	Concentrations Range (mg/cu m)	Number of Samples	Reference
Acetone	Acryloid	620	-	1	129
"	Injection molding	<2	-	-	130
"	Plastics cleaning	-	<118-493	5	131
"	Solvent	17	5-40	8	132
"	Fiberglass plant	76	15-324	26	133
"	Rifle scope production	982-summer 444-fall	625-1550 94-1677	44 29	134
"	Vinyl installation	185	128-216	3	136
"	Spray painting	40	-	-	136
Methyl ethyl ketone	Label printing	<1	-	8	135
"	Baseball bat manufacturing	9	3-15	11	137
"	Painting	4	ND-35	11	138
"	Parts cleaning	196	44-413	7	138
"	Ski plant	209 55 79	18-968 <1-230 ND-162	12 5 4	139 139 139
"	Painting	6	ND-21	-	140
"	Cementing	26	6-68	8	132
"	Spray painting	<30	-	-	136
"	Reinforced plastics plant	0.8	ND-33	47	141
"	Gasket cleaning	339	233-395	3	142
"	Paint plant	182	38-1441	21	143
Methyl butyl ketone	"	54	46-66	3	143
Methyl isobutyl ketone	Television cabinet manufacturing	4	<4-45	30	128
"	Spray painting	<40	-	-	136
"	Paint plant	104	39-197	12	143
Diacetone alcohol	Aerosol can production	114	18.5-265	30	144

*ND=non-detected

ketones from those present when cases of peripheral neuropathy were found in 1973 [146]. Methyl n-butyl ketone concentrations (84 samples) were all below the detection limit (0.01 mg/cu m) of the analytical method. Methyl ethyl ketone concentrations averaged 99 mg/cu m for 84 samples with a range from 7 to 388 mg/cu m. Methyl isobutyl ketone concentrations averaged 18 mg/cu m for 84 samples with a range of less than 0.01 mg/cu m to 108 mg/cu m. Methyl n-butyl ketone use had been discontinued following the episode of peripheral neuropathy, and methyl ethyl and methyl isobutyl ketones were substituted. All methyl ethyl ketone and methyl isobutyl ketone concentrations reported in April 1977 were below 388 and 108 mg/cu m, respectively.

Engineering Controls

Engineering controls should be designed to keep airborne ketones at concentrations at or below the permissible exposure limits. Closed systems, preferably under lower pressure than uncontaminated areas and properly operated and maintained, should be used wherever appropriate, for example, in the manufacture of the ketones and in their use as intermediate chemicals. Frequent tests must be conducted for leaks in such a closed system. Where closed systems are not feasible, well-designed local exhaust ventilation systems should be used. Guidance for design of ventilation systems can be found in Industrial Ventilation--A Manual of Recommended Practice [147] and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971 [148]. Continuous local exhaust ventilation or some means of ketone containment (such as cooling coils)

should be used when ketones are used in open tanks and during their charging or discharging.

Ventilation systems require regular inspection to provide the necessary level of employee protection. Airflow should be measured on a frequent, regular basis, at least every 3 months. Continuous monitoring can be provided by the installation of oil or water manometers. The desired airflow can be indicated on the manometer to provide ready reference for a quick determination of optimum performance.

Electrical systems used in processes in which ketones are used, handled, or processed should conform to the National Electrical Code [149]. Motors used for ventilation systems or material transfer must be explosion-proof when ketones classified as flammable liquids (mesityl oxide, acetone, methyl n-butyl ketone, methyl ethyl ketone, methyl isobutyl ketone, and methyl n-propyl ketone) are present. Explosion-proof motors should also be used with the other ketones, which are all classified as combustible liquids. Concentrations of ketones in the exhaust system must be kept below the lower flammable limit for the particular ketone. Airmovers in exhaust systems where ketone concentrations may exceed one fourth of the lower explosive limit must be of sparkproof construction. Data on flashpoints and lower explosive limits are included in Table XI-2.

Storage facilities for the ketones must conform to the requirements for storing flammable and combustible liquids as stated in 29 CFR 1910.106. Many of the lower boiling ketones form flammable air-vapor mixtures in the spaces of a storage tank at normal temperatures unless air is excluded. Inert gas can be used to exclude air. If air is not excluded, a flame arrestor should be installed on the tank vent [150]. Storage tanks should

be electrically bonded and grounded and should be diked to contain leaks. Diked areas should be equipped with a sump pump (non-sparking) to remove any spilled ketone. Steel piping and tanks are adequate for storing most ketones up to 2 months and when product quality is not unusually critical. For longer storage or critical purity, a steel tank may have to be lined, eg, with an inorganic zinc silicate coating [150].

V. WORK PRACTICES

The 12 ketones included in this document present different toxicologic problems; however, they also have many common properties that require similar work practices. Although all 12 ketones are liquids at room temperature (Table XI-2), some have high vapor pressure, and, therefore, employees may contact ketones by inhaling vapor or mist as well as by having their skin or eyes come in contact with the liquid. There is some evidence that skin absorption, at least of some ketones, may also occur [43,45]. All ketones are good lipid solvents and thus cause dermatitis whether or not they can penetrate the skin. Engineering controls and work practices should be designed and implemented to maintain concentrations of airborne ketones at or below permissible exposure limits, minimize excursions, prevent skin and eye contact, and reduce fire and explosion hazards.

The ketones have been shown to be a significant fire hazard. All of them have flashpoints below 200 F (Table XI-2) and are therefore classified as combustible or flammable liquids of Classes IA, IB, IC, II, and IIIA according to the criteria in 29 CFR 1910.106a. Boiling points and flashpoints for the 12 ketones are listed in Table XI-2.

A flammable liquid has a flashpoint below 100 F (37.8 C). The classes of flammable liquids are IA, liquids with a flashpoint below 73 F (22.8 C) and boiling point below 100 F; IB those with a flashpoint below 73 F and boiling point at or above 100 F; and IC, those with a flashpoint at or above 73 F (22.8 C) and below 100 F (37.8 C). Combustible liquids have flashpoints above 100 F and are divided into two classes. Those in Class

II have a flashpoint at or above 100 F and below 140 F, and those in Class III have a flashpoint above 140 F. Combustible liquids in Class IIIA have flashpoints at or above 140 F and below 200 F, and those in IIIB have flashpoints at or above 200 F. If ventilation is adequate to maintain the concentrations of ketones at or near their permissible exposure limits, which are based on toxicologic considerations, the potential for fire and explosion will be eliminated. However, elevated concentrations can be caused by vapor accumulation above a liquid surface, in depressions, at container openings, and at vent openings. The employer should be familiar with the particular properties of the ketone in use and should provide instructions for safely handling that ketone. All ignition sources, such as fire, sparks, and smoking, must be prohibited when and where ketones are handled, used, or stored. The National Fire Protection Association (NFPA) Standard #77, "Static Electricity," lists precautions to be taken to prevent the accumulation of static electricity which may be a source of ignition. Precautions include bonding, grounding, and humidity control.

Equipment for handling ketones should be properly bonded, grounded, and installed according to local and state building codes. Only sparkproof tools may be used with the ketones that are classified as flammable liquids, and it is a good practice to use them with all ketones. Outside storage areas are preferred to inside areas, but storage containers should always be protected from direct sunlight and from other sources of heat. Only containers and tanks designed to contain flammable or combustible liquids should be used for transporting or storing large amounts of ketones.

Detailed regulations for handling flammable and combustible liquids are found in 29 CFR 1910.106. These rules have been adapted from the NFPA. Areas covered include tank storage; piping, valves, and fittings; containers and portable tank storage; and industrial uses.

When fighting fires involving ketones, personnel must use protective equipment similar to that worn whenever there may be the danger of breathing hazardous products of combustion. Carbon dioxide or dry chemical extinguishers are most effective for extinguishing ketone fires. Water spray may also be used, but a water hose stream which can scatter the burning liquid should not. Larger spills or tank fires are best controlled with "alcohol type" foam [151,152]. When entering an area for firefighting, personnel should wear a self-contained breathing apparatus operated in the positive-pressure mode.

Closed system operations, when compatible with the use of the ketone, present the best means of protecting the worker from ketone exposure. When workers carefully observe good, preventive maintenance and frequently inspect systems for leaks, spills, and worn parts, closed systems are effective in minimizing exposure to ketones. When leaks do occur, they must promptly be repaired by trained workers wearing the appropriate protective clothing and respiratory protection.

Ketones are powerful degreasing agents and are capable of causing or aggravating skin irritation after prolonged or repeated exposure. Although the use of personal protective equipment is not an adequate substitute for good work practices and ventilation, in some cases it is necessary. Resistant gloves and clothing, safety goggles (with 20-cm minimum face shields if full-face protection is necessary), aprons, coats, and boots

should be worn when needed to prevent prolonged or repeated skin contact with ketones. If clothing becomes soaked with a ketone, it is important that the clothing be removed immediately and not be reused until it is free of contamination. The prompt removal of clothing will not only lessen the chance for skin irritation but will also minimize the risk of burns, since clothing contaminated with ketones is readily flammable. Clothing may be decontaminated by laundering or by allowing the clothing to dry. (Clothing must be dried in a suitably ventilated area.) Laundry personnel must also be informed of any hazards to them and must be protected from ketone exposure. Foot burns may result if some ketones (acetone, for example [151]) with high vapor pressures are spilled into shoes and the shoes are not thoroughly cleaned and ventilated after contamination.

The employer should be aware that not all rubber or plasticized gloves are adequate protection from ketones. McFee [153] and Sansone and Tewari [154] have investigated gloves' resistance to acetone and methyl ethyl ketone penetration. The data, as shown in Table V-1, indicate that only milled butyl gloves offer protection for long periods and several (neoprene, polyvinyl chloride, and nitrile) may not be adequate even for short, half-hour usage. Employers must determine that gloves supplied for skin protection are adequate and provide the necessary protection for the particular ketone.

Although engineering controls are required to prevent or contain major spills, minor spills may also present a hazard and should be promptly cleaned up by personnel properly protected against the inhalation of and prolonged skin contact with ketones. These precautions will minimize the risk of fire and also reduce the spread of vapors into confined spaces or

TABLE V-1

EXTENT OF SOLVENT PENETRATION (%) THROUGH GLOVE MATERIALS

Glove Material	Glove Thickness (mm)	Penetration after 30 minutes		Penetration after 24 hours	Reference
		Acetone	Methyl ethyl ketone	Acetone	
Natural rubber	0.4	0.1-1	1-10	-	154
	0.18	-	-	41	153
Neoprene	0.4	1-10	>10	-	154
	0.18	-	-	83.4	153
Natural rubber and neoprene	0.5	0.1-1	1-10	-	154
	0.30	-	-	50	153
Polyvinyl chloride	0.2	>10	>10	-	154
	0.51-0.69	-	-	90	153
Polyvinyl alcohol	0.4	<0.1	<0.1	-	154
	0.74	-	-	3.6	153
Nitrile	0.4	>10	>10	-	154
Milled butyl	0.48	-	-	<0.3	153

into those located below ground level. Rags, mops, and other materials contaminated with a ketone or used to clean up a spill must be stored in a closed metal container until they can be removed from the work area and properly cleaned or disposed of.

Ketones and materials contaminated with ketones must be disposed of according to applicable Federal, state, and local regulations. The preferred method is to recover and reuse the ketone if possible. Incineration or burial in a proper land fill are other methods of disposal. Ketone disposal in sewers should be prohibited since vapors may still be ignited.

Under some conditions, ketones may collect in low and confined spaces. Confined-space entry procedures must be developed and enforced to prevent exposure from exceeding the permissible exposure limit in an enclosed or confined space. The atmosphere should be checked for the presence of ketones, sufficient oxygen, and toxic materials as may be necessary. Where ketones are present or where their absence cannot be assured, workers should wear proper equipment when entering an enclosed or confined space. The following protective measures are also required: use of a lifeline and harness, communication with an observer properly equipped to rescue, and the presence of a third party ready to lend assistance. Before entering a tank or confined space, every worker must obtain a permit signed by an authorized person stating that the atmosphere has been checked and found safe or stating that all necessary safety precautions have been observed.

Employees should never use ketones to remove grease and dirt from their hands. Employers should provide washrooms and showers where mild

soap can be used to remove dirt and grease. If soap and water are not effective, the employer should provide an alternative means of removal, such as a waterless cleanser. The employees should also wash their hands following contact with any ketone; this procedure will minimize the risk of irritation. The requirements for sanitation facilities are listed in 29 CFR 1910.141.

Eyewash fountains and emergency showers must be provided for immediate emergency use in work areas where employees may come in contact with ketones at excessive concentrations. The requirements for emergency eyewash fountains and showers, as well as for medical and first aid, are detailed in 29 CFR 1910.151. Emergency equipment must be useable and sanitary at all times.

Engineering controls are the first choice in reducing exposure to ketone vapors. Work practices, such as those discussed in this chapter, may also significantly reduce exposure. Respirators are the least satisfactory means of preventing inhalation exposure to ketones, but there are situations, such as during the installation or testing of new exhaust systems, during performance of nonroutine maintenance or repair, during single operations, or during emergencies, when they represent the only feasible and adequate source of protection. When respirators are required, the employer should ensure that only respirators approved by NIOSH or MSHA are used. Respirator selection should follow the guidelines indicated in Table I-2. Respirators certified for use at higher concentrations may always be used at lower concentrations. Dust respirators are not suitable for protection against ketone vapors and offer only poor protection. Compressed oxygen should not be used when there is danger of contact with

flammable liquids, vapors, or sources of ignition, especially in confined spaces [151].

Since some ketones can cause eye irritation, the use of half-mask facepiece respirators has been restricted. Data presented in Tables III-1 and III-8 suggest that eye irritation will occur at concentrations less than 10 times the proposed limit of each ketone except methyl n-butyl ketone and isophorone.

Evidence to support the use of air purifying (cartridge or canister) respirators was not found. Air purifying respirators can only be safely used when knowledge of the absorbent's capacity for the ketone is available and where an indication of breakthrough (end-of-service-life indicators or smell and taste properties) is available at non-hazardous concentrations. Nelson and Harder [155] have conducted respirator cartridge efficiency studies. The test concentration was 1,000 ppm, the flowrate 53.3 liters/minute, humidity 50%, and the temperature 20-22 C. These data show that the useful life of cartridges is limited to 1-2 hours, and they highlight the need to get more definitive data for breakthrough at other concentrations. End-of-service-life indicators for cartridges do not yet exist for the ketones, and, therefore, warnings of breakthrough are dependent on odor or taste. Odor threshold values, to provide an adequate margin of safety, must be no more than three times the recommended environmental limit. It seems probable that the odor of some of these ketones can be detected at such concentrations, but the reliability of detection, the rapidity of odor fatigue, and the variation in the population are not known.

In all workplaces where ketones or ketone-containing substances must be handled, written instructions informing employees of the particular hazards involved, the method of handling, procedures for cleaning up spilled material, personal protective equipment to be worn, and procedures for emergencies must be posted, on file, and available to employees. The employer must establish a program of instruction that will ensure that all potentially exposed employees are familiar with the procedures. The Material Safety Data Sheet described in Appendix II may be used as a guide for employers in providing the necessary information. The duties of employees involved in maintenance and repair activities pose special problems of potential contact and exposure, especially in work on enclosed systems or in operations involving ventilation-system repair and maintenance. The nature of this type of work increases the potential for exposure. Maintenance employees may not be sufficiently familiar with the hazardous materials with which they are involved. Therefore, special supervisory control and work practice precautions are required to prevent exposure of these employees.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

(a) Acetone

In 1945, Cook [156] compiled a list of maximum allowable concentrations (MAC's) for industrial atmospheric contaminants. He noted that the California Industrial Accident Commission, the Oregon State Board of Health, and the Massachusetts Department of Labor and Industries recommended a 500-ppm (1,180 mg/cu m) MAC for exposure to acetone, while the Utah Department of Health used a 200-ppm (474 mg/cu m) MAC and the New York State Department of Labor used a 1,000-ppm (2,370 mg/cu m) MAC as the guidelines for exposure to acetone. Cook recommended 1,000 mg/cu m as a tentative limit for occupational exposure to acetone. This recommendation was based on the findings of Nelson and coworkers [15], who reported that, at a concentration of 500 ppm (1,180 mg/cu m), acetone caused eye, nose, and throat irritation in humans exposed for 3-5 minutes.

In 1946, the Subcommittee on Threshold Limits of the American Conference of Governmental Industrial Hygienists (ACGIH) [157] adopted a list entitled "Maximum Allowable Concentrations of Air Contaminants for 1946," which included a 500-ppm (1,180-mg/cu m) MAC for acetone as noted by Cook [156].

In 1948, the designation of the environmental limit was changed from an MAC to a TLV (Threshold Limit Value), but the value remained at 500 ppm (1,180 mg/cu m) for acetone [158]. In 1953, the ACGIH [159] defined a TLV as the "maximum average atmospheric concentration of contaminants to which workers may be exposed for an eight-hour working day without injury to

health," and it adopted a TLV of 1,000 ppm (2,370 mg/cu m) for acetone. No justification for the change in the limit was reported at that time, but the basis for the change was presented in the 1962 ACGIH Documentation of Threshold Limit Values [160], which cited reports by Nelson et al [15], Lehmann and Flury [57], and Vigliani and Zurlo [28]. Nelson et al [15] stated that, although acetone caused slight irritation at 300 ppm (711 mg/cu m), most humans tolerated exposure at 500 ppm (1,180 mg/cu m). Lehmann and Flury [57] noted a fatal acetone poisoning in a 12-year-old child who wore a damp acetone dressing. Vigliani and Zurlo [28] found chronic inflammation of the respiratory tract in workers exposed to acetone at 1,000 ppm (2,370 mg/cu m) for 3 hours daily for 7-15 years, and complaints of dizziness were reported. Since 1958, the 2,400 mg/cu m TLV was referred to as a time-weighted average (TWA) concentration for a normal workday [161].

In 1966, the ACGIH Committee on Threshold Limit Values [162] questioned whether the exposure of workers to acetone reported by Vigliani and Zurlo [28] was "pure." The level has remained at 2,400 mg/cu m since 1953 [163]. Review of the more detailed study [27] of the workers, however, does not confirm the suspicion that exposures were mixed.

In 1976, the ACGIH [164] proposed a Threshold Limit Value-Short Term Exposure Level (TLV-STEL) for acetone of 3,000 mg/cu m. The ACGIH defined the TLV-STEL as the "maximal concentration to which workers can be exposed for a period up to 15 minutes continuously without suffering from 1) intolerable irritation, 2) chronic or irreversible tissue change, or 3) narcosis of sufficient degree to increase accident proneness, impair self-rescue, or materially reduce work efficiency, provided that no more than

four excursions per day are permitted, with at least 60 minutes between exposure periods, and provided that the daily TLV-TWA also is not exceeded."

Occupational exposure limits to ketones in other countries are listed in Table VI-1 [165].

The current US Federal standard for occupational exposure to acetone is 2,400 mg/cu m (1,000 ppm) as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard was based on the TLV adopted by ACGIH in 1968 [166].

(b) Methyl Ethyl Ketone

In 1945, Cook [156] noted that a limit for methyl ethyl ketone exposure in workplaces of 500 ppm (1,470 mg/cu m) was recommended by the California Industrial Accident Commission and a 300-ppm (882 mg/cu m) limit was used as a guideline by the Massachusetts Department of Labor and Industries. Cook recommended 500 mg/cu m as a tentative limit, because of the nose and throat irritation experienced by humans exposed at 350 ppm (1,032 mg/cu m) [15]. He also cited the work of Patty et al [19] that showed no "serious disturbance" in guinea pigs exposed to methyl ethyl ketone at 0.3% by volume for a few hours.

In 1946, the ACGIH [157] adopted a 200-ppm (588 mg/cu m) MAC for methyl ethyl ketone. In 1948, the ACGIH [158] adopted a 250-ppm (735 mg/cu m) limit for methyl ethyl ketone when the designation was changed from an MAC to a TLV. No justification for this change was reported at that time. This TLV was retained until 1961, when the ACGIH [167] lowered the TLV as a TWA concentration to 590 mg/cu m. The basis for this recommendation was provided in the 1962 ACGIH documentation [160], which included the reports

TABLE VI-1

OCCUPATIONAL EXPOSURE LIMITS (MG/CU M) OF KETONES

Countries	Acetone	Methyl Ethyl Ketone	Methyl n-Propyl Ketone	Methyl n-Butyl Ketone	Methyl n-Amyl Ketone	Methyl Isobutyl Ketone	Methyl Isoamyl Ketone	Diisobutyl Ketone	Cyclo-hexanone	Mesityl Oxide	Diacetone Alcohol	Isophorone
Australia	2,400	590	700	410	465	410	475	150	200	100	240	140
Belgium	2,400	590	700	410	-	410	475	150	200	100	240	25
Bulgaria	-	200	200	-	-	-	-		10			
Czechos-lovakia	800	-	-	-	-	-	-	-	200	-	-	-
Finland	2,400	590	700	410	465	410	475	150	200	100	240	55
German Democratic Republic	1,000	300	-	-	-	-	-	-	-	-	-	-
Federal Republic of Germany	2,400	590	700	410	-	400	-	290	200	100	240	28
Hungary	200	200	-	-	-	-	-	-	-	-	-	-
Italy	1,000	400	-	-	-	300	-	150	200	-	-	-
Japan	480	590	-	-	-	410	-	-	100	-	-	-
Netherlands	2,400	590	700	100	-	410	475	150	200	100	240	25
Poland	200	200	100	200	-	200	-	-	20	20	-	5
Romania	1,000	200	250	200	-	200	-	150	100	100	150	50
Sweden	1,200	440	-	-	-	210	-	-	-	-	-	-
Switzerland	2,400	590	700	410	-	410	475	150	200	100	240	25*
USSR	200	200	200	-	-	-	-	-	10	1**	-	-
Yugoslavia	800	200	700	410	465	410	-	290	200	100	240	140
United States												
1978 Federal Standards (29 CFR 1910.1000)	2,400	590	700	410	465	410	-	290	200	100	240	140
NIOSH Recommended Exposure Limits	590	590	530	4	465	200	230	140	100	40	240	23

*Ceiling value
**Skin irritant

Adapted from reference 165

of Patty et al [19] and Nelson et al [15], cited earlier. In addition, Smith and Mayers [33] found that dermatitis and numbness in the arms occurred in humans exposed to methyl ethyl ketone vapor at 300-600 ppm (882-1,760 mg/cu m).

The TLV has remained the same since 1961 [163]. In 1976, the ACGIH [164] proposed, in addition to the existing TLV-TWA, a TLV-STEL of 885 mg/cu m.

The current US Federal standard for occupational exposure to methyl ethyl ketone is 590 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV of 1968 adopted by ACGIH [166].

(c) Methyl n-Propyl Ketone

In 1945, in his list of MAC's for atmospheric contaminants, Cook [156] noted that the California Industrial Accident Commission recommended a 500-ppm (1,760 mg/cu m) MAC for exposure to methyl n-propyl ketone in the workplace and the Utah Department of Health recommended a 1,500-ppm (5,280 mg/cu m) MAC. Cook [156] considered 1,000 mg/cu m to be a tentative concentration limit for occupational exposure to methyl n-propyl ketone. This conclusion was based on the results of an inhalation study with guinea pigs by Yant and associates [52], who reported that guinea pigs exposed at 0.15 vol% for 810 minutes exhibited little or no effects and that short exposures to methyl n-propyl ketone at 0.15% by volume were irritating to humans.

In 1946, the Subcommittee on Threshold Limits of the ACGIH [157] adopted a 200-ppm (704 mg/cu m) MAC for methyl n-propyl ketone. No justification for this level was reported. In 1948, the designation of the

limit was changed from an MAC to a TLV, but the value remained at 200 ppm (704 mg/cu m) [158].

In the 1962 documentation [160], the ACGIH presented the basis for their TLV as a TWA concentration of 700 mg/cu m. It referred to the inhalation study by Yant et al [52] on guinea pigs exposed to methyl n-propyl ketone at 0.15% by volume for several hours. The guinea pigs showed little or no effect from the exposure. In 1966, the ACGIH [162] still considered the 700 mg/cu m TLV "low enough to prevent onset of narcosis and irritation."

The ACGIH, in the 1974 documentation [168], cited the findings of Specht et al [34] and of Yant and associates [52]. Specht et al reported that, when exposed to methyl n-propyl ketone at 0.25% by volume, guinea pigs exhibited irritation and weakness, and coma resulted in animals exposed at 0.50% by volume.

The current US Federal standard for occupational exposure to methyl n-propyl ketone is 700 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV adopted by the ACGIH in 1968 [166].

(d) Methyl n-Butyl Ketone

In 1945, Cook [156] recommended 500 mg/cu m as a tentative MAC for exposure to methyl n-butyl ketone in the workplace. This recommendation was based on findings by Schrenk et al [169] about the responses of guinea pigs and humans to methyl n-butyl ketone vapor. The guinea pigs had no abnormal signs during or after an exposure to methyl n-butyl ketone at 0.1% by volume for 810 minutes. However, humans exposed at that concentration for a few minutes noted a strong odor and developed eye and nose

irritation. Cook [156] derived the 500 mg/cu m limit for prolonged exposure by arbitrarily making it one-fourth of the concentration at which there was irritation.

In 1946, the Subcommittee on Threshold Limits [157] adopted the 200-ppm (820 mg/cu m) MAC for methyl n-butyl ketone recommended by Cook [156]. In 1947, the MAC was reduced to 100 ppm (410 mg/cu m), but no reason was given [170]. In 1948, when the designation of an MAC was changed to a TLV, the limit remained at 100 ppm (410 mg/cu m) [158]. In the 1962 documentation [160], ACGIH cited the study of guinea pig and human responses conducted by Schrenk et al [169] to justify setting the TLV as a TWA concentration at 410 mg/cu m.

In 1966, the ACGIH [162] once again recommended the TLV as a TWA concentration of 410 mg/cu m for exposure to methyl n-butyl ketone and cited the study of Specht et al [34] in the 1966 ACGIH documentation. Specht and his coworkers found that guinea pigs developed progressive narcosis leading to coma and death when they were exposed to methyl n-butyl ketone at concentrations of 0.13, 0.6, and 1.2% by volume for 12, 7, and 4 hours, respectively. The ACGIH considered the TLV of 410 mg/cu m sufficient to "provide protection against irritation and, by a large margin, against initiation of narcosis." The same information was reported in the 1974 ACGIH documentation [168]. In 1976, the ACGIH [164] adopted a TLV-TWA of 100 mg/cu m with a proposed TLV-STEL of 150 mg/cu m.

The current US Federal standard for occupational exposure to methyl n-butyl ketone is 410 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the ACGIH's TLV set in 1968 [166].

(e) Methyl n-Amyl Ketone

In 1971, the ACGIH [171] adopted a TLV of 465 mg/cu m as a TWA concentration for methyl n-amyl ketone, stating that the limit "should be low enough to prevent onset of narcosis and to serve as a guide for practical control." The level was based on a recommendation by Rowe and Wolf [9], who had reviewed the data from an inhalation exposure study on guinea pigs by Specht et al [34]. Mucous membrane irritation occurred at a concentration of 0.15% by volume, narcotic effects were apparent at 0.20% by volume, and, at 0.48% by volume, narcosis and death resulted in guinea pigs exposed for 4-8 hours. In 1976, the ACGIH [164] proposed a 710 mg/cu m TLV-STEL in addition to the TLV-TWA.

The current US Federal standard for occupational exposure to methyl n-amyl ketone is 465 mg/cu m (100 ppm) as an 8-hour TWA concentration limit (29 CFR 1910.1000).

(f) Methyl Isobutyl Ketone

In 1945, Cook [156] recommended an MAC of 200 ppm as a tentative concentration limit for exposure to methyl isobutyl ketone in workplaces. This recommendation was based on Specht's [59] inhalation study of guinea pigs which showed that, at a concentration of 0.1% by volume, methyl isobutyl ketone caused nose and eye irritation in a man but was well tolerated by the guinea pigs.

In 1946, the Subcommittee on Threshold Limits of the ACGIH [157] adopted the 200-ppm (820 mg/cu m) MAC for methyl isobutyl ketone recommended by Cook [156]. In 1948, the designation of the limit was changed from an MAC to a TLV, and the ACGIH [158] lowered the limit to 100 ppm (410 mg/cu m). The justification for this reduction was not reported

at the time. In addition to citing Specht's findings [59], the ACGIH in their 1962 documentation mentioned the report of Silverman and coworkers [16] as justification for the TLV of 410 mg/cu m. Silverman et al [16] found that most people exposed to methyl isobutyl ketone at 200 ppm (820 mg/cu m) experienced eye irritation. They concluded that 100 ppm (410 mg/cu m) was a sensory response limit and that most people experimentally exposed to 100 ppm found this limit acceptable for an 8-hour exposure. In 1966, the ACGIH [162] stated that the TLV as a TWA concentration of 410 mg/cu m "should be sufficiently low to permit exposures without eye irritation during the working day." This statement was based on the previously mentioned studies. [59,16].

The ACGIH has retained the TLV-TWA of 410 mg/cu m [164]. In 1976, the ACGIH [164] proposed a 510 mg/cu m TLV-STEL in addition to the TLV-TWA.

The current US Federal standard for occupational exposure to methyl isobutyl ketone is 410 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the ACGIH's 1968 TLV for methyl isobutyl ketone [166].

(g) Methyl Isoamyl ketone

In 1971, the Committee on Threshold Limit Values of the ACGIH [171] adopted a TLV of 460 mg/cu m for methyl isoamyl ketone. The Committee assumed that the toxicities of methyl isoamyl ketone and methyl isobutyl ketone would be similar because their structures are similar. In the 1971 documentation [171], the ACGIH recommended a TLV of 460 mg/cu m as a TWA concentration to protect against eye irritation to methyl isoamyl ketone in the workplace. The limit was based on information from Rowe and Wolf [9],

who stated that 100 ppm (466 mg/cu m) was well below the concentration at which methyl isobutyl ketone produced narcotic effects.

At present, there is no Federal standard for occupational exposure to methyl isoamyl ketone in the United States.

(h) Diisobutyl Ketone

In 1956, the ACGIH [172] recommended a TLV of 50 ppm (290 mg/cu m) for occupational exposure to diisobutyl ketone. The basis for this recommendation was not published at that time. A study by Carpenter et al [20] on animals' responses to exposure of diisobutyl ketone was cited in 1962 documentation [160] by ACGIH. Carpenter and colleagues [20] found that at 125 ppm (726 mg/cu m) the vapor had no adverse physiologic effects on rats and guinea pigs exposed for 7 hours/day for 30 days. However, the guinea pigs exposed at 250 ppm (1,450 mg/cu m) for the same duration had a decrease in liver weight. According to Carpenter et al, humans considered exposure at 50 ppm (290 mg/cu m) for 8 hours to be "satisfactory." The TLV of 290 mg/cu m was designated as a TWA concentration.

In the 1971 documentation [171], the ACGIH included a study by Silverman and associates [16], describing the sensory response to industrial solvent vapors, to substantiate the recommendation that 290 mg/cu m was a concentration at which "no toxic effects will occur and irritation should be minimal." Silverman et al reported that humans exposed to diisobutyl ketone above 50 ppm (290 mg/cu m) experienced eye irritation and an unpleasant odor.

In 1973, the ACGIH [173] recommended a lower TLV as a TWA concentration, 150 mg/cu m, for exposure to diisobutyl ketone. In the 1974 documentation [168], the ACGIH again cited the studies of Carpenter et al

[20] and Silverman et al [16] to justify the recommended TLV as one that should prevent eye irritation from exposure to diisobutyl ketone.

The current US Federal standard for occupational exposure to disobutyl ketone is 290 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV adopted by ACGIH in 1968 [166].

(i) Cyclohexanone

In 1945, Cook [156] recommended a tentative MAC of 400 mg/cu m for exposure to cyclohexanone in workplaces. This tentative value was based on the experimental human exposure study by Nelson and his associates [15] and the exposure study of rabbits by Treon et al [54]. At a concentration of 75 ppm (301 mg/cu m), Nelson et al [15] noted that cyclohexanone caused eye, nose, and throat irritation in humans exposed for 3-5 minutes. Treon et al [54] found that, at a concentration of 0.75 mg/liter (750 mg/cu m) in air, cyclohexanone induced degenerative changes in the liver and kidneys of rabbits exposed for fifty 6-hour periods.

In 1946, the Subcommittee on Threshold Limits of the ACGIH [157] adopted the 100-ppm (401 mg/cu m) MAC for cyclohexanone recommended by Cook [156].

In 1948, the designation of the limit was changed from an MAC to a TLV [158], but the level remained at 100 ppm (401 mg/cu m) for cyclohexanone through 1960 [174]. In 1961, the ACGIH [167] recommended a lower TLV of 200 mg/cu m as a TWA concentration. The justification was included in the 1962 documentation [160], in which the ACGIH referred to a report by Treon et al [54] stating that 0.75 mg/liters (750 mg/cu m) was just above the maximal safe level for rabbits. Nelson and associates [15]

reported that throat irritation was the most marked effect on humans exposed to cyclohexanone at 50 ppm (200 mg/cu m) for 3-5 minutes. Most subjects in their study were able to tolerate exposure to cyclohexanone at 25 ppm (100 mg/cu m).

The TLV of 200 mg/cu m as a TWA concentration remained unchanged [163,166,175]. However, the ACGIH, in 1974 documentation [168], stated that, although 200 mg/cu m "is recommended as the TLV, some complaints of irritation may be raised by some unaccustomed individuals at this level. It should provide a good margin of safety against systemic effects because concentrations that might be harmful are not likely to be tolerated."

In 1976, the ACGIH [164] proposed a TLV-STEL of 200 mg/cu m in addition to the TLV-TWA.

The current US Federal standard for occupational exposure to cyclohexanone is 200 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV adopted by the ACGIH in 1968 [166].

(j) Mesityl Oxide

In 1942, Smyth and coworkers [21] reported that no adverse effects occurred in animals exposed to mesityl oxide vapor at 50 ppm (201 mg/cu m) for thirty 8-hour exposures. They found that mesityl oxide at 250-500 ppm (1,000-2,010 mg/cu m) had primarily narcotic effects on guinea pigs and rats, and they concluded that it might cause damage to the lungs, liver, and kidneys [21]. In 1945, Cook [156] recommended an MAC value of 200 mg/cu m as a tentative limit for exposure to mesityl oxide in the workplace. He used the report of Smyth et al [21] to substantiate his recommendation. The ACGIH Committee on Threshold Limits [157] adopted 50

ppm (201 mg/cu m) as the recommended environmental limit in 1946, as proposed by Cook.

In 1948, the ACGIH [158] recommended a limit of 50 ppm (201 mg/cu m), although the designation was changed from an MAC to a TLV. The TLV value remained at 50 ppm (201 mg/cu m) until 1958, when the ACGIH [16] lowered it to 100 mg/cu m. No reason for this change was given at that time. The ACGIH, in the 1962 documentation [160], cited a study of human sensory response conducted by Silverman et al [16] showing eye irritation at 25 ppm (100 mg/cu m) and nose irritation at 50 ppm (200 mg/cu m), to justify the TLV as a TWA concentration of 100 mg/cu m for mesityl oxide. Some subjects found that the odor was objectionable at 50 ppm (201 mg/cu m) and that they had a persistent, unpleasant taste that remained for 3-6 hours after the exposure [16]. The level has remained at 100 mg/cu m for mesityl oxide since 1972 [164]. In 1976, the ACGIH [164] proposed a TLV-STEL of 100 mg/cu m.

The current US Federal standard for occupational exposure to mesityl oxide is 100 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard was based on the 1968 TLV adopted by the ACGIH [166].

(k) Diacetone Alcohol

In 1955, the ACGIH [176] established a tentative TLV of 50 ppm (237 mg/cu m) for occupational exposure to diacetone alcohol. No basis for recommending this level was reported at that time. The ACGIH later provided the justification for this level in the 1962 documentation [160], where the studies of Silverman et al [16] and Von Oettingen [177] were discussed. Silverman and associates [16] reported that, at a concentration

of 100 ppm (474 mg/cu m), the vapor of diacetone alcohol caused eye, nose, and throat irritation in humans. They concluded that 50 ppm (237 mg/cu m) was a "more reliable limit." Von Oettingen [177] reported that restlessness, irritation of the mucous membranes, and excitement followed by drowsiness were observed in mice, rats, rabbits, and cats exposed to diacetone alcohol vapor at 2,100 ppm (10,000 mg/cu m). The ACGIH [160] concluded: "In view of eye, nose and throat irritation occurring in persons exposed to 100 parts per million, a value of 50 parts per million is suggested." The TLV of 239 mg/cu m as a TWA concentration has not been changed by the ACGIH [162,163,168].

The current US Federal standard for occupational exposure to diacetone alcohol is 240 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV adopted by the ACGIH in 1968 [166].

(1) Isophorone

In 1945, Cook [156] recommended a tentative value of 100 mg/cu m as an MAC for exposure to isophorone in the workplace. This tentative value was based on an inhalation study with guinea pigs and rats by Smyth and coworkers [21]. The animals were exposed to isophorone vapor for thirty 8-hour exposures at concentrations of 25-500 ppm (140-2,800 mg/cu m) [21]. The exposures at 25 ppm (140 mg/cu m) had no adverse effects on rats and guinea pigs.

In 1946, the ACGIH [157] recommended an MAC of 25 ppm (140 mg/cu m) which was based on the recommendation by Cook [156]. In 1948, the designation of the limit changed from an MAC to a TLV, and the 25-ppm (140 mg/cu m) limit was again recommended by the ACGIH [158]. The ACGIH, in the

1962 documentation [160], cited a report by Smyth et al [58] of the warning properties of isophorone vapor in humans exposed for a few minutes at concentrations of 40-400 ppm (230-2,300 mg/cu m). Eye, nose, and throat irritation was reported at all concentrations, and nausea, headache, dizziness, faintness, intoxication, and a feeling of suffocation occurred in a few subjects at concentrations of 200 ppm (1,130 mg/cu m) and 400 ppm (2,300 mg/cu m). The ACGIH [162] established a TLV of 140 mg/cu m to prevent irritative and narcotic effects, stating that the level was well below the concentration at which systemic effects might occur.

The ACGIH cited a study by Silverman and coworkers [16] on human sensory response to isophorone in the 1966 documentation [162]. Eye, nose, and throat irritation was experienced by subjects exposed to isophorone vapor at 25 ppm (140 mg/cu m). However, the TLV as a TWA concentration was not changed from 140 mg/cu m [162].

In the 1971 documentation [171], the ACGIH included the comments by Rowe and Wolf [9] that impure commercial products containing appreciable amounts of material more volatile than isophorone were used in the studies by Smyth and coworkers [21] and Smyth and Seaton [58] and, therefore, that the results should not be considered in evaluating the hazards of exposure to isophorone. Rowe and Wolf [9] recommended a lower TLV of 10 ppm (56 mg/cu m).

In 1972, the ACGIH [178] recommended that the TLV for isophorone be lowered. A ceiling TLV of 28 mg/cu m was recommended and documented in 1974 documentation [168]. GD Ware (written communication, June 1973) reported to the ACGIH that fatigue and malaise were experienced by employees exposed to isophorone at 5-8 ppm (28-45 mg/cu m) for 1 month.

This study found that, when the concentrations were lowered to 1-4 ppm (6-23 mg/cu m) with exhaust ventilation, complaints about such effects were no longer made.

The current US Federal standard for occupational exposure to isophorone is 140 mg/cu m as an 8-hour TWA concentration limit (29 CFR 1910.1000). This standard is based on the TLV adopted by the ACGIH in 1968 [166].

Basis for the Recommended Standard

Many workers are exposed to small amounts of airborne ketones or have negligible contact with these compounds. Under these conditions, many provisions of the recommended standard need not be complied with since they are intended to protect workers' health under hazardous circumstances. Concern for workers' health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit, so NIOSH has defined the action level as one-half of the recommended environmental limit. Occupational exposure is defined as exposure above the action level. This definition delineates those work situations that do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. The action level has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from potentially hazardous areas.

(a) Permissible Exposure Limits

Because all of these ketones are CNS depressants, exposure to several of them, even at or below the recommended workplace environmental concentration, might produce additive effects. Employers should consider

these additive effects when simultaneous exposures to several ketones, or to ketones and other CNS depressants, occur. The following formula can be used to determine compliance with the recommended TWA environmental limits when such additive effects may occur:

$$\frac{C1}{PEL1} + \frac{C2}{PEL2} + \frac{C3}{PEL3} + \ldots + \frac{Cn}{PELn} \leq 1$$

where:

C = the concentration of a substance

PEL = the permissible exposure limit of that substance

Peripheral neuropathy caused by methyl n-butyl ketone is the most serious known form of occupational illness from these ketones. Although narcosis may result from exposure to all of these ketones at high concentrations, irritation of the eyes, nose, and throat occurs first and should act as a warning property.

Studies have indicated that the high molecular weight ketones in a homologous series are more irritating and have a stronger narcotic action. Therefore, the higher molecular weight ketones of a homologous series should have exposure limits that are less than those of the low molecular weight ketones when toxicity is based solely on irritation.

(1) Acetone (1 ppm = 2.37 mg/cu m)

Eight workers exposed to acetone at concentrations above 12,000 ppm had throat and eye irritation, weakness in the legs, and headache [25]. One worker fainted; several felt dizzy and lightheaded. The symptoms and urinary acetone levels indicate that even a short exposure to acetone at concentrations above 12,000 ppm is hazardous.

Six studies have reported possible adverse effects on humans from acetone at concentrations at and below 1,000 ppm. In one study [17], exposure at an average concentration of 1,000 ppm for 8 hours resulted in headaches and lightheadedness in some workers. A second study [28] indicated that exposure to acetone at 1,000 ppm for 3 hours/day for 7-15 years and at 700 ppm for an unreported length of time resulted in inflammation of the respiratory tract, stomach, and duodenum, occasional dizziness, and loss of strength. In a third study [27], which may have been the basis for part of the data in the second study, employees exposed to acetone at 307-918 ppm (730-2,180 mg/cu m) had irritation of the eyes, nose, throat, and lungs and CNS disturbances. In addition, these investigators presented evidence that daily 6-hour exposures to acetone at 833 ppm (2,000 mg/cu m) did lead to an accumulation in the body, which persisted into the next workday. A fourth report [18] revealed that several subjects experienced irritation of the eyes, nose, and throat, tension, general weakness, heavy eyes, or lack of energy the morning after 6 hours of exposure to acetone at 1,000 ppm. This study also found the same complaints in those exposed at 500 ppm for 6 hours and the same but fewer complaints in those exposed at 250 ppm for 6 hours. These results are consistent with those in a fifth report [15] in which acetone at 350 ppm for 3-5 minutes caused irritation of the eyes, nose, and throat in a majority of 10 subjects exposed to it. In this report it was also noted that at 300 ppm there was slight irritation and that most of the 10 volunteers estimated 200 ppm was the highest concentration that would be satisfactory for an 8-hour exposure. A sixth study [42] indicated that employee volunteers who were exposed to acetone for 2 or 4 hours, with

exercise in some cases, suffered no untoward effects and had no symptoms after exposure at 100 ppm, a finding consonant with that in another paper [18] in which none of five young men exposed for 6 hours at 100 ppm in an unstressed situation complained of any adverse reaction.

From the above six studies, it is apparent that untoward effects have occurred at 1,000 ppm and have become decreasingly severe as the concentration decreases. As the concentrations of acetone have decreased below 200 ppm, few or no complaints of adverse reactions have occurred.

One report [42], in which an unreported number of men (probably four or less) were unaffected by acetone at 500 ppm for between 2 and 4 hours, seems to be inconsistent with the trend indicated by the results of other exposures. It is unclear whether a longer exposure, such as that during a normal 8-hour workday, would have resulted in adverse reactions similar to those seen in the other five studies; however, it is clear from this report that acetone did accumulate in the body and that some of it would probably remain to the next workday.

The preponderance of exposure data at concentrations of 1,000 ppm and less leads to the conclusion that some untoward effects will occur in those exposed to acetone at concentrations below 500 ppm. Furthermore, the available evidence indicates that occupational exposure to acetone may lead to its accumulation in the body. It seems reasonable to conclude that a workplace environmental limit of about 250 ppm (590 mg/cu m) should be established. Therefore, it is recommended that acetone concentrations in the workplace air not exceed 250 ppm (590 mg/cu m) as a TWA concentration limit for up to a 10-hour workshift in a 40-hour workweek.

(2) Methyl Ethyl Ketone (1 ppm = 2.95 mg/cu m)

Nelson et al [15] reported that most volunteers exposed to methyl ethyl ketone estimated that 200 ppm (590 mg/cu m) would be satisfactory for an 8-hour exposure. However, at 100 ppm, slight nasal irritation and throat irritation were produced, while at 200 ppm it caused mild eye irritation in some subjects. At 350 ppm (1,030 mg/cu m), methyl ethyl ketone irritated the eyes, nose, and throat of most subjects.

Patty et al [19] detected no serious disturbances in guinea pigs exposed to methyl ethyl ketone at 3,000 ppm (8,850 mg/cu m) for a few hours. In animals, methyl ethyl ketone did not produce any signs of peripheral neuropathy [73,74,77]. However, animals exposed to a combination of methyl n-butyl ketone and methyl ethyl ketone developed paralysis in a much shorter period of time than did animals exposed to only methyl n-butyl ketone [73]. Couri et al [87] presented evidence that methyl ethyl ketone may potentiate the toxicity of methyl n-butyl ketone by stimulating the metabolic activation of the latter ketone.

Schwetz et al [97] found some evidence of teratogenicity when pregnant rats were exposed to methyl ethyl ketone at 1,126 and 2,618 ppm (3,320 and 7,720 mg/cu m). However, as discussed in Chapter III, it is not clear that this evidence can be reliably extrapolated to humans. In addition, the possible potentiation of neurotoxicity induced by methyl n-butyl ketone should be handled by stringent control of methyl n-butyl ketone rather than by regulating methyl ethyl ketone for possible effects. A review of the available data provides no basis for a change in the present Federal workplace environmental limit of 200 ppm (590 mg/cu m). Therefore, it is recommended that methyl ethyl ketone concentrations in the

workplace air not exceed 200 ppm (590 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(3) Methyl n-Propyl Ketone (1 ppm = 3.52 mg/cu m)

Specht et al [34] found that methyl n-propyl ketone was considerably less toxic than methyl n-butyl ketone but more toxic than methyl ethyl ketone in guinea pigs. Narcosis was produced in guinea pigs exposed at 5,000 ppm (17,600 mg/cu m). Interpretation of the data of Specht et al suggests that methyl n-propyl ketone might be more irritating to the eyes, nose, and throat than was either acetone or methyl ethyl ketone.

It is believed that an extrapolation from the data of Specht et al [34] to the findings of Nelson et al [15] is appropriate. Nelson et al reported that 100 ppm (350 mg/cu m) of methyl ethyl ketone produced slight irritation in volunteers. Interpretation of the data of Specht et al [34], as mentioned before, suggests that methyl n-propyl ketone is at least as irritating as methyl ethyl ketone. Thus, it is believed that a slight reduction in the current Federal standard of 700 mg/cu m (200 ppm) is warranted to protect employees from irritation to the eyes, nose, and throat. Therefore, an exposure limit for methyl n-propyl ketone of 150 ppm (530 mg/cu m) for up to a 10-hour TWA concentration in a 40-hour workweek is recommended.

(4) Methyl n-Butyl Ketone (1 ppm = 4.10 mg/cu m)

Allen et al [37] found 81 cases of peripheral neuropathy, 11 of which were diagnosed as moderate to severe, in a coated-fabric plant where methyl n-butyl ketone and methyl ethyl ketone were used. Employees who worked at or near the print machines, where both ketones were used as

solvents, had a significantly higher incidence of neuropathy than did employees who worked in other departments. Analysis of the areas around the print machine showed methyl n-butyl ketone at 9.2-36 ppm (38-148 mg/cu m) and methyl ethyl ketone at 331-516 ppm (1,360-2,115 mg/cu m) when 9 of 17 machines were in operation. No neuropathy was found in a similar plant that used methyl ethyl ketone without methyl n-butyl ketone.

In 1976, Mallov [39] investigated peripheral neuropathy in three spray painters. The onset of neuropathy correlated with the substitution of methyl n-butyl ketone in a paint formulation for methyl isobutyl ketone and methyl isoamyl ketone. Although no environmental sampling or analysis was reported, Mallov stated that the three workers had ample opportunity for exposure to methyl n-butyl ketone by inhalation and skin absorption.

Studies on a variety of animals have conclusively demonstrated that repeated exposure to methyl n-butyl ketone produced peripheral neuropathy [70,71,73,179]. A comparison of data indicated that the no effect concentration for methyl n-butyl ketone in animals was probably less than 100 ppm [76,77,80].

Exposure concentrations at the coated-fabric plant varied over a considerable range, so it is difficult to interpret which concentrations were safe and which were not. While methyl n-butyl ketone at higher concentrations probably caused the neuropathy, a review of the data of Billmaier et al [38] indicates that apparently 2.3 ppm (9.4 mg/cu m) cannot be ruled out. Because of the severity of the toxic effects and the incomplete reversibility of the lesions in these fabric workers, a cautious approach which views the lowest concentration as a possible toxic concentration is needed and a recommendation for a very low environmental

limit seems appropriate. Thus, a limit at least as low as 1 ppm (4 mg/cu m) is recommended, pending the development of suitable data that will allow a more rigorous development of a permissible limit.

Inasmuch as methyl n-butyl ketone penetrates skin, it might be interpreted that percutaneous absorption played a significant, conceivably even the predominant, part in the development of neuropathy in the fabric workers. This interpretation is supported by evidence that the workers washed their hands in the ketone solution. However, a study of the relevant data does not support this interpretation. Calculations based on quantitative data on percutaneous absorption [45] and some assumptions about likely immersion times (see Chapter III, Correlation of Exposure and Effect for an example of these calculations) suggest that percutaneous absorption was less important than inhalation in what was undoubtedly a dose-related neuropathogenesis. However, the ability of this ketone to penetrate skin as well as to cause local skin effects is sufficiently evident to warrant work practices to prevent skin contact. It is recommended, therefore, that methyl n-butyl ketone concentrations in workplace air not exceed 1 ppm (4 mg/cu m) as a 10-hour TWA concentration.

(5) Methyl n-Amyl Ketone (1 ppm = 4.67 mg/cu m)

Specht et al [34] found that methyl n-amyl ketone at 1,500 ppm (7,000 mg/cu m) produced irritation of the mucous membranes of guinea pigs. At 2,000 ppm, it was strongly narcotic, and 4-8 hours of exposure at 4,800 ppm (22,400 mg/cu m) produced narcosis and death. Because repeated exposure of rats and monkeys to methyl n-amyl ketone did not produce any evidence of peripheral neuropathy, it is believed that the standard for this ketone should be based on its irritating properties.

As was the case for methyl n-propyl ketone, methyl n-amyl ketone was also more irritating than acetone and methyl ethyl ketone [34]. Because methyl n-amyl ketone was at least as irritating to animals as methyl n-propyl ketone [34], the recommended exposure limit should be at least as low as that for methyl n-propyl ketone. However, the concentration at which methyl n-amyl ketone does not produce irritation in humans was not found. Therefore, there is no basis for a change in the present Federal workplace environmental limit of 100 ppm (465 mg/cu m). It is therefore recommended that the concentration of methyl n-amyl ketone in workplace air not exceed 100 ppm (465 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek. It seems probable that this exposure limit should prevent most irritation in workers exposed to methyl n-amyl ketone.

(6) Methyl Isobutyl Ketone (1 ppm = 4.10 mg/cu m)

Silverman et al [16] reported that 100 ppm was the highest concentration that most volunteers estimated to be satisfactory for an 8-hour exposure. At 200 ppm, the eyes of most persons were irritated. Specht [59] reported that methyl isobutyl ketone at 1,000 ppm (4,100 mg/cu m) was exceedingly irritating to the eyes and nose of the investigator during an experiment in which guinea pigs showed little disturbance. Linari et al [30] reported that methyl isobutyl ketone at 80-500 ppm produced weakness, loss of appetite, headache, eye irritation, sore throat, stomach ache, nausea, and vomiting in exposed workers. In a followup study, Armeli et al [31] reported that these signs were reduced to the point of disappearing in workers exposed to methyl isobutyl ketone at 50-105 ppm (205-430 mg/cu m); however, a few workers still had CNS and

gastrointestinal disorders. It seems probable that the effects noted in these few workers resulted from exposures at the higher concentrations.

Spencer et al [71] reported that rats exposed to methyl isobutyl ketone at 1,500 ppm for 5 months developed minimal neuropathologic changes in the most distal portions of the tibial and ulnar nerves. The authors related these findings to the presence of 3% methyl n-butyl ketone as a contaminant of the methyl isobutyl ketone. In a later study, Spencer et al [74] reported that purified methyl isobutyl ketone (9 % purity) did not cause peripheral neuropathy in animals.

Because of the studies of Silverman et al [16], Linari et al [30], and Armeli et al [31], it is believed that the current Federal standard for methyl isobutyl ketone of 410 mg/cu m (100 ppm) is not adequate to protect employees from adverse effects, but the concentration at which methyl isobutyl ketone will produce no adverse effects is not known. The study of Armeli et al [31] indicated that the adverse effects were virtually eliminated when the concentration of airborne methyl isobutyl ketone was reduced to 50-105 ppm. Thus, it is recommended that the concentration of methyl isobutyl ketone in the workplace air not exceed 50 ppm (200 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(7) Methyl Isoamyl Ketone (1 ppm = 4.67 mg/cu m)

Currently, there is no information to firmly support a limit for methyl isoamyl ketone. Because methyl isoamyl ketone contains one more carbon atom than does methyl isobutyl ketone, methyl isobutyl ketone might produce irritation and narcosis at concentrations at least as low as those at which methyl isobutyl ketone produces these effects. Therefore, a limit of 50 ppm (230 mg/cu m), corresponding to that of methyl isobutyl ketone,

is proposed for up to a 10-hour TWA concentration in a 40-hour workweek.

(8) Diisobutyl ketone (1 ppm = 5.82 mg/cu m)

Two volunteers had slight irritation of the eyes and nose when exposed to diisobutyl ketone at 100 ppm (582 mg/cu m) [20]. Another person had slight tearing and two others had headaches at the same concentration. Two of the subjects exposed at 50 ppm (290 mg/cu m) experienced transitory, slight irritation of the eyes and nose at the beginning of the exposure. However, Carpenter et al [20] stated that the vapor could be smelled and tasted throughout the exposure period. All three subjects exposed at 100 ppm estimated that a workplace atmosphere of 100 ppm would be unsatisfactory for continuous exposure. Silverman et al [16] reported that 25 ppm (145 mg/cu m) was the highest concentration that most subjects considered satisfactory for an 8-hour exposure to diisobutyl ketone. Because of these findings, it is recommended that to reduce eye irritation, the concentration of diisobutyl ketone in workplace air not exceed 25 ppm (140 mg/cu m) for up to a 10-hour TWA concentration in a 40-hour workweek.

(9) Cyclohexanone (1 ppm = 4.01 mg/cu m)

Nelson et al [15] reported that 25 ppm (100 mg/cu m) was the highest concentration that most subjects considered satisfactory for an 8-hour exposure to cyclohexanone. At 50 ppm, throat irritation was reported, while, at 75 ppm (300 mg/cu m), most subjects had irritation of the eyes, nose, and throat.

Cyclohexanone at 190 ppm (762 mg/cu m) for fifty 6-hour exposures produced liver and kidney damage in rabbits [54]. Cutaneous or subcutaneous application of cyclohexanone produced cataracts in guinea pigs [66]. In some cases, lens damage was reversed within 3 months after

exposure. No such findings in humans have been reported (see discussion in paragraph (c) of this section). Because of the findings of Nelson et al [15], and because of the ability of cyclohexanone to produce liver and kidney damage at relatively low concentrations in rabbits, it is recommended that the exposure limit for cyclohexanone be set at 25 ppm (100 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(10) Mesityl Oxide (1 ppm = 4.01 mg/cu m)

Silverman et al [16] reported that the majority of volunteers exposed to mesityl oxide for 15 minutes had eye irritation at 25 ppm and nose irritation at 50 ppm (200 mg/cu m). Smyth et al [21] reported that mesityl oxide at 50 ppm had no adverse affects on rats and guinea pigs exposed for thirty 8-hour periods. An extrapolation of the data of Smyth et al to humans might indicate that repeated exposures to mesityl oxide at 50 ppm would be safe. However, eye irritation was reported at 25 ppm (100 mg/cu m), and there is reason to believe that eye irritation by mesityl oxide is more serious than that produced by the lower ketones. (See Correlation of Exposure and Effect.) In addition, systemic effects (liver and kidney changes) occurred in animals exposed (at higher concentrations) to mesityl oxide. Thus, it is recommended that the concentration of mesityl oxide in workplace air not exceed 10 ppm (40 mg/cu m) as a TWA concentration for up to a 10-hour workshift in a 40-hour workweek.

(11) Diacetone Alcohol (1 ppm = 4.75 mg/cu m)

Silverman et al [16] reported that most subjects had eye irritation and all subjects had nose and throat irritation when exposed to diacetone alcohol at 100 ppm (475 mg/cu m) [16]. The highest concentration

of diacetone alcohol judged to be satisfactory for an 8-hour exposure was 50 ppm. Lehmann and Flury [57] found irritation of mucous membranes and somnolence in a variety of experimental animals exposed to diacetone alcohol at 2,100 ppm (9,975 mg/cu m). Kidney injury was also reported in rabbits at that concentration. To prevent eye irritation, an exposure limit for diacetone alcohol of 50 ppm (240 mg/cu m) for up to a 10-hour TWA concentration in a 40-hour workweek is recommended. This is identical to the present Federal standard.

(12) Isophorone (1 ppm = 5.65 mg/cu m)

Silverman et al [16] reported that 10 ppm was the highest concentration that most volunteers considered satisfactory for an 8-hour exposure. They noted that irritation of the eyes, nose, and throat was produced in the majority of persons exposed at 25 ppm.

Smyth et al [21] exposed animals to isophorone for 8 hours/day, 5 days/week, for 6 weeks. They reported that isophorone at 25 ppm produced no adverse effects. In six animals exposed at 50 ppm, the liver of one and the kidneys of four were affected; the nature of these changes was not described. All of 20 animals survived exposures at 50 ppm, but 2 of 16 died after exposure at 100 ppm.

GD Ware (written communication, June 1973) of Western Electric Company reported to the TLV Committee of the ACGIH that workers suffered fatigue and malaise after exposure to isophorone at 5-8 ppm. When air levels were reduced to 1-4 ppm, no further complaints were received. (A copy of this letter to the TLV Committee has been furnished to NIOSH.) Based on this information, a permissible exposure limit of 4 ppm (23

mg/cu m) as a TWA concentration for up to a 10-hour workshift, 40-hour workweek is recommended.

(b) Sampling and Analysis

The recommended sampling method, reviewed in more detail in Chapter IV, involves collecting airborne ketones in charcoal-filled tubes, followed by desorption with carbon disulfide. Gas-liquid chromatography is the recommended analytic procedure. The sampling method was chosen because it has been validated for 11 of the ketones and because it is expected to provide adequate collection efficiency for airborne ketones. The gas-chromatographic method of analysis was selected because it is sensitive and relatively simple to use, although it is not entirely specific for ketones. Other compounds having the same retention time as the ketone being analyzed will interfere with the analysis; however, mass spectrometry can be used to identify some of the eluted compounds.

(c) Medical Surveillance

Because repeated exposure to methyl n-butyl ketone can produce peripheral neuropathy [37,39,70-72,74], electrodiagnostic examinations including electromyography and nerve conduction and velocity measurements must be made available to workers exposed to this ketone. These types of electrodiagnostic studies are objective tests which are the most sensitive indicators of early peripheral neuropathy. Employees' weight should also be monitored, since unexpected weight loss may be an advanced indicator of peripheral neuropathy. Exposure to the 12 ketones can also irritate the eyes, nose, and throat. These effects should be considered in medical examinations of exposed employees. Furthermore, because acetone and cyclohexane have produced cataracts in experimental animals, particular

attention should be given to the eyes where exposure to these substances may occur [66]. Although the evidence of kidney and liver damage [30,54,55,57] was developed from exposures at high concentrations or, in the case of animal studies, at high doses, and thus not weighed heavily in developing environmental limits, workers' kidney and probably liver functions should be monitored. Therefore, periodic urinalysis is proposed as a requirement, and periodic monitoring of liver enzymes is proposed as an additional recommendation.

(d) Personal Protective Equipment and Clothing

Because these ketones are defatting agents that can cause skin irritation and dermatitis, workers who are likely to have skin contact with the liquid ketones must wear protective gloves. The use of safety goggles or face shields (20-cm minimum) is recommended to prevent eye irritation when contact of ketones with the eyes is likely. Other personal protective equipment should include respirators when necessary, and appropriate protective clothing. The types of respiratory protective devices described in Tables I-2 should be those approved under the provisions of 30 CFR 11.

(e) Informing Employees of Hazards

Personnel in areas where a ketone is present must be advised of the adverse effects of exposure and informed of the signs and symptoms of the disorders. Employees exposed to methyl n-butyl ketone should be warned that the neurotoxic symptoms of this ketone may have an insidious onset. A continuing education program is an important part of a preventive hygiene program for employees occupationally exposed to ketones. Properly trained persons should periodically inform employees about the dangers of improper work practices, such as washing their hands with ketones, and of exposure

by other routes, such as inhalation and ingestion. Additionally, employees should be informed of engineering controls and work practices used to limit exposure and of the environmental and medical monitoring practices for checking control procedures and determining the health status of employees.

(f) Work Practices

Procedures that minimize the volatilization of ketones and workers' contact with ketones should be used for the cleanup of spills, waste disposal, general housekeeping, and storage of ketones. Personal hygienic measures should be adopted to prevent ingestion of ketones and to further reduce the probability of skin contact. Work practices that will prevent ingestion and limit inhalation or skin contact with ketones must be implemented. Smoking, eating, and food preparation should be prohibited in areas where ketones are present. Spilled ketones must be cleaned up promptly by trained personnel wearing adequate protective equipment and clothing. Employees must be prohibited from washing their hands with ketones, and handwashing facilities must be provided. If contamination of clothing with ketones is likely, employees should wear protective outer garments. Because of the adverse effects associated with exposure to ketones, entry into areas where there is occupational exposure to ketones should be restricted to authorized persons.

(g) Monitoring and Recordkeeping

Industrial hygiene surveys should be made to determine in which areas there may be occupational exposure to ketones. Thereafter, where there is occupational exposure to ketones, the exposure of each employee should be determined, and the workplace air in the breathing zones of employees in every operation should be sampled and analyzed at least every 3 months.

Changes in production or process necessitate additional monitoring to detect any changes in the concentrations of airborne ketones.

The Toxic Substances Control Act of 1976 requires that "Records of...adverse reactions to the health of employees shall be retained for thirty years from the date such reactions were first reported to or known by the person maintaining such records...." Because medical examinations will often provide the first recognized evidence of an adverse reaction, whether at the time of the examination or retrospectively, it appears consonant with the Toxic Substances Control Act to require medical records on ketone workers to be maintained for 30 years. Furthermore, records of environmental exposures should be kept for the same period, to allow correlation of a ketone worker's exposure with his or her health.

VII. RESEARCH NEEDS

No detailed epidemiologic studies of the effects of occupational exposure to ketones other than methyl n-butyl ketone have been found in the literature. Such studies are needed to determine chronic effects of ketone exposure on humans and safe levels of such exposures.

An investigation of potential neurotoxic effects of ketones other than methyl n-butyl ketone is needed. Such studies are needed to determine if any other ketones can produce peripheral neuropathy in exposed workers. Studies are also necessary to gather information on the toxicity of metabolites and on relevant toxic interactions with other chemicals. In this connection, NIOSH is currently (1978) investigating evidence of peripheral neuropathy in an operation involving exposure to methyl ethyl ketone and toluene. Studies in animal models are needed to examine possible neurotoxic effects from mixed exposures. Also, since methyl ethyl ketone has been shown to enhance the toxicity of methyl n-butyl ketone, the possibility of a toxic interaction between methyl ethyl ketone and other chemicals should be explored.

Further studies are needed to discover whether these ketones have carcinogenic, mutagenic, or teratogenic effects.

Preliminary conclusions regarding the potential of acetone and cyclohexanone to cause cataracts have been made based on animal data. Retrospective morbidity studies of workers exposed to ketones should be performed to determine the cataract-causing potential in humans.

Although studies on the concentrations of ketones that produced irritation of the eyes, nose, and throat were found, not all of the ketones

were tested. Research is required to determine the concentrations of ketones that produce irritation. Investigations should also be conducted to determine the concentrations of ketones that can produce impaired judgment.

Information concerning the resistance to ketone penetration of personal protective devices, such as gloves and clothing, is needed.

VIII. REFERENCES

1. Lurie AP: Ketones, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1967, vol 12, pp 101-69

2. Dohogne A: [Solvent (continuation)--Ketones and ketone-alcohols.] Rev Tech Ind Cuir 61:224-30, 1969 (Fre)

3. Lowenheim FA, Moran MK: Faith, Keyes, and Clark's Industrial Chemicals, ed 4. New York, John Wiley and Sons, 1975, pp 21-25,304-09,539-46

4. Von Oettingen WF: Acetone and Its Homologues. Geneva, International Labour Office, 1939, 6 pp

5. Miller RJ: Acetone, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1965, vol 1, pp 159-67

6. Appendix 7--Laboratory analyses and observations--Normal or usual results when no disease is recognized, in Stedman's Medical Dictionary, ed 22. Baltimore, Williams and Wilkins Co, 1972, pp 1459-66

7. Preliminary Report on U.S. Production of Selected Synthetic Organic Chemicals--Preliminary Totals, 1976, S.O.C. Series No. C/P-77-1. US International Trade Commission, Mar 1977, 9 pp

8. Acetone, in Chemical Economics Handbook. Menlo Park, Calif, SRI International, Jan 1975, pp 604.5031B,604.5032A to 604.5032C

9. Rowe VK, Wolf MA: Ketones, in Patty FA (ed.): Industrial Hygiene and Toxicology, ed 2 rev; Toxicology (Fassett DW, Irish DD, eds.) New York, Interscience Publishers, 1963, vol 2, pp 1719-70

10. Methyl isobutyl ketone--Methyl isobutyl carbinol, in Chemical Economic Handbook. Menlo Park, Calif, SRI International, June 1975, pp 675.6030A to 675.6030E

11. Hawley GG (ed.): The Condensed Chemical Dictionary, ed 8. New York, Van Nostrand Reinhold Co, 1971, p 576

12. Kralovec RD, Louderback HB: Cyclohexanol and cyclohexanone, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1965, vol 6, pp 683-88

13. Synthetic Organic Chemicals--United States Production and Sales, 1975, USITC publication No. 804. US International Trade Commission, 1977, pp 21,30

14. Synthetic Organic Chemicals--United States Production and Sales of Miscellaneous Chemicals, 1975--Preliminary. US International Trade Commission, Sept 1976, pp 5-11

15. Nelson KW, Ege JF JR, Ross M, Woodman LE, Silverman L: Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 25:282-85, 1943

16. Silverman L, Schulte HF, First MW: Further studies on sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 28:262-66, 1946

17. Raleigh RL, McGee WA: Effects of short, high-concentration exposures to acetone as determined by observation in the work area. J Occup Med 14:607-10, 1972

18. Matsushita T, Yoshimune A, Inoue T, Yamaka S, Suzuki H: [Experimental studies for determining the maximum permissible concentrations of acetone--1. Biological reactions in one-day exposure to acetone.] Jpn J Ind Health 11:477-85, 1969 (Jap)

19. Patty FA, Schrenk HH, Yant WP: Acute response of guinea pigs to vapors of some new commercial organic compounds--VIII. Butanone. US Public Health Rep 50:1217-28, 1935

20. Carpenter CP, Pozzani UC, Weil CS: Toxicity and hazard of diisobutyl ketone vapors. Arch Ind Hyg Occup Med 8:377-81, 1953

21. Smyth HF Jr, Seaton J, Fischer L: Response of guinea pigs and rats to repeated inhalation of vapors of mesityl oxide and isophorone. J Ind Hyg Toxicol 24:46-50, 1942

22. Cossmann: [Acetone intoxication after application of a mull-celluloid dressing.] Muench Med Wochenschr 36:1556-57, 1903 (Ger)

23. Harris LC, Jackson RH: Acute acetone poisoning caused by setting fluid for immobilizing casts. Br Med J 2:1024-26, 1952

24. Cesaro AN, Pinerolo A: [Percutaneous absorption of acetone.] Med Lav 38:384-87, 1947 (Ita)

25. Ross DS: Acute acetone intoxication involving eight male workers. Ann Occup Hyg 16:73-75, 1973

26. Criteria for a Recommended Standard....Occupational Exposure to 1,1,1-Trichloroethane (Methyl Chloroform), HEW publication No. (NIOSH) 76-184. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, NIOSH, National Institute for Occupational Safety and Health, 1976, 179 pp

27. Parmeggiani L, Sassi C: [Occupational poisoning with acetone--Clinical disturbances, investigations in work rooms and physiopathological research.] Med Lav 45:431-68, 1954 (Ita)

28. Vigliani EC, Zurlo N: [Experiences of the Clinics del Lavoro with some maximum concentrations of poisons of industry at the place of work (MAK).] Arch Gewerbepathol Gewerbehyg 13:528-34, 1955 (Ger)

29. Gitelson S, Werczberger A, Herman JB: Coma and hyperglycemia following drinking of acetone. Diabetes 15:810-11, 1966

30. Linari F, Perrelli G, Varese D: [Clinical observations and blood chemistry tests among workers exposed to the effect of a complex ketone--Methyl-isobutyl ketone.] Arch Sci Med, 1964, pp 226-37 (Ita)

31. Armeli G, Linari F, Martorano G: [Clinical and hematochemical examinations in workers exposed to the action of a ketone (MIBK) repeated after five years.] Lav Um 20:418-24, 1968 (Ita)

32. Lupulescu AP, Birmingham DJ: Effect of protective agent against lipid-solvent-induced damages--Ultrastructural and scanning electron microscopical study of human epidermis. Arch Environ Health 31:33-36, 1976

33. Smith AR, Mayers MR: Study of poisoning and fire hazards of butanone and acetone. NY State Ind Bull 23:174-76, 1944

34. Specht H, Miller JW, Valaer PJ, Sayers RR: Acute Response of Guinea Pigs to the Inhalation of Ketone Vapors, NIH bulletin No. 176. Federal Security Agency, Public Health Service, National Institute of Health, 1940, 66 pp

35. Berg EF: Retrobulbar neuritis--A case report of presumed solvent toxicity. Ann Ophthalmol 3:1351-53, 1971

36. Viader F, Lechevalier B, Morin P: [Toxic polyneuritis in a plastic worker--Possible implication of methyl ethyl ketone.] Nouv Presse Med 4:1813-14, 1975 (Fre)

37. Allen N, Mendell JR, Billmaier DJ, Fontaine RE, O'Neill J: Toxic polyneuropathy due to methyl n-butyl ketone. Arch Neurol 32:209-18, 1975

38. Billmaier D, Yee HT, Allen N, Craft B, Williams N, Epstein S, Fontaine R: Peripheral neuropathy in a coated fabrics plant. J Occup Med 16:665-71, 1974

39. Mallov JS: MBK neuropathy among spray painters. J Am Med Assoc 235:1455-57, 1976

40. Flink EB: Heavy metal poisoning, in Beeson PB, McDermott W (eds.): Cecil-Loeb Textbook of Medicine, ed 13. Philadelphia, WB Saunders Co, 1971, pp 61-69

41. Davenport JG, Farrell DF, Sumi SM: "Giant axonal neuropathy" caused by industrial chemicals--Neurofilamentous axonal masses in man. Neurology 26:919-23, 1976

42. DiVincenzo GD, Yanno FJ, Astill BD: Exposure of man and dog to low concentrations of acetone vapor. Am Ind Hyg Assoc J 34:329-36, 1973

43. Munies R, Wurster DE: Investigation of some factors influencing percutaneous absorption--III. Absorption of methyl ethyl ketone. J Pharm Sci 54:1281-84, 1965

44. Wurster DE, Kramer SF: Investigation of some factors influencing percutaneous absorption. J Pharm Sci 50:288-93, 1961

45. DiVincenzo GD, Hamilton ML, Kaplan CJ, Krasavage WJ, O'Donoghue FL: Studies on the respiratory uptake and excretion and the skin absorption of methyl n-butyl ketone in humans and dogs. Submitted for publication in Toxicol Appl Pharmacol.

46. Craft BF: An incident of industrially related toxic peripheral neuropathy. Report presented before the Seminar on Early Warning Systems for Toxic Substances, Seattle, Jan 30-Feb 1, 1974, 9 pp

47. Fontaine RE, Lemen R, Heath CW: Peripheral Neuropathy--Columbus, Ohio, EPI report No. 74-39-2. Unpublished report submitted by US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Atlanta, Oct 10, 1974, 15 pp

48. Schlomovitz BH, Seybold EG: The toxicity of the "acetone bodies"--I. Acetone administered intravenously. Am J Physiol 70:130-39, 1924

49. Salant W, Kleitman N: Pharmacological studies on acetone. J Pharmacol Exp Ther 19:293-306, 1922

50. Sollmann T: Studies of chronic intoxication on albino rats--II. Alcohols (ethyl, methyl and "wood") and acetone. J Pharmacol Exp Ther 16:291-309, 1920-1921

51. Walton DC, Kehr EF, Loevenhart AS: A comparison of the pharmacological action of diacetone alcohol and acetone. J Pharmacol Exp Ther 33:175-83, 1928

52. Yant WP, Patty FA, Schrenk HH: Acute response of guinea pigs to vapors of some new commercial organic compounds. Public Health Rep 51:392-99, 1936

53. MacEwen JD, Vernot EH, Haun CC: Effect of 90-day Continuous Exposure to Methylisobutylketone on Dogs, Monkeys and Rats. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1971, 23 pp (NTIS AD 730 291)

54. Treon JF, Crutchfield WE Jr, Kitzmiller KV: The physiological response of animals to cyclohexane, methylcyclohexane, and certain derivatives of these compounds--II. Inhalation. J Ind Hyg Toxicol 25:323-47, 1943

55. Hart ER, Schick JA, Leake CD: The toxicity of mesityl oxide. Univ Calif Berkeley Publ Pharmacol 1:161-73, 1939

56. Carpenter CP, Smyth HF Jr, Pozzani UC: The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 31:343-46, 1949

57. Ketones, in Lehmann KB, Flury F (eds.): Toxicology and Hygiene of Industrial Solvents (King E, Smyth HF Jr, Transl). Baltimore, Williams and Wilkins Co, 1943, pp 243-48,254

58. Smyth HF Jr, Seaton J: Acute response of guinea pigs and rats to inhalation of the vapors of isophorone. J Ind Hyg Toxicol 22: 477-83, 1940

59. Specht H: Acute response of guinea pigs to inhalation of methyl isobutyl ketone. Public Health Rep 53:292-300, 1938

60. Specht H, Miller JW, Valaer PJ: Acute response of guinea pigs to the inhalation of dimethyl ketone (acetone) vapor in air. Public Health Rep 54:944-54, 1939

61. Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC, Striegel JA: Range-finding toxicity data--List VI. Am Ind Hyg Assoc J 23:95-107, 1962

62. Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC: Range-finding toxicity data--List V. Arch Ind Hyg Occup Med 10:61-68, 1954

63. Smyth HF Jr, Carpenter CP, Weil CS: Range-finding toxicity data--List IV. Arch Ind Hyg Occup Med 4:119-22, 1951

64. Smyth HF Jr, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS: Range-finding toxicity data--List VII. Am Ind Hyg Assoc J 30:470-76, 1969

65. 4-Methyl-3-penten-2-one, in Hann RW Jr, Jensen PA: Water Quality Characteristics of Hazardous Materials. College Station, Texas A and M University, Civil Engineering Department, Environmental Engineering Division, 1974, 2 pp

66. Rengstorff RH, Petrali JP, Sim VM: Cataracts induced in guinea pigs by acetone, cyclohexanone, and dimethyl sulfoxide. Am J Optom Arch Am Acad Optom 49:308-19, 1972

67. Carpenter CP, Smyth HF Jr: Chemical burns of the rabbit cornea. Am J Ophthalmol 29:1363-72, 1946

68. Truhaut R, Dutertre-Catella H, Phu-Lich N: [Toxicity study of an industrial solvent--Isophorone--Its irritating effect on the skin and mucous membranes.] J Eur Toxicol 5:31-37, 1972 (Fre)

69. Draize JH, Woodard G, Calvery HO: Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 82:377-90, 1944

70. Mendell JR, Saida K, Ganansia MF, Jackson DB, Weiss H, Gardier RW, Chrisman C, Allen N, Couri D, O'Neill J, Marks B, Hetland L: Toxic polyneuropathy produced by methyl n-butyl ketone. Science 185:787-89, 1974

71. Spencer PS, Schaumburg HH, Raleigh RL, Terhaar CJ: Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch Neurol 32:219-22, 1975

72. Raleigh RL, Spencer PS, Schaumburg HH: Methyl n-butyl ketone. J Occup Med 17:286, 1975

73. Saida K, Mendell JR, Weiss HS: Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J Neuropathol Exp Neurol 35:207-25, 1976

74. Spencer PS, Schaumburg HH: Feline nervous system response to chronic intoxication with commercial grades of methyl n-butyl ketone, methyl isobutyl ketone, and methyl ethyl ketone. Toxicol Appl Pharmacol 37:301-11, 1976

75. Spencer PS, Schaumburg HH: Ultrastructural studies of the dying-back process--IV. Differential vulnerability of PNS and CNS fibers in experimental central-peripheral distal axonopathies. J Neurolpathol Exp Neurol 36:300-20, 1977

76. Krasavage WJ, O'Donoghue JL, Terhaar CJ: Chronic Inhalation Exposure of Rats to Methyl n-Butyl Ketone (MnBK). Report Submitted to NIOSH by Eastman Kodak Co, Rochester, NY, Jan 1977, 38 pp

77. DeJesus PV, Pleasure DF, Asbury, AK, Brown MJ, Paradise CM: Effects of Methyl Butyl Ketone on Peripheral Nerves and Its Mechanism of Action, Contract No. PENN CDC 99-76-16. New Haven, Conn, Yale University, and West Haven, Conn, Veterans Administration Hospital, 1977, 40 pp

78. Schaumburg HH, Spencer PS: Environmental hydrocarbons produce degeneration in cat hypothalamus and optic tract. Science 199:199-200, 1978

79. Goldberg ME, Johnson HE, Pozzani UC, Smyth HF Jr: Effect of repeated inhalation of vapors of industrial solvents on animal behavior. Am Ind Hyg Assoc J 25:369-75, 1964

80. Johnson BL, Setzer JV, Lewis TR, Anger WK: Effects of methyl n-butyl ketone on behavior and the nervous system. Am Ind Hyg Assoc J 38:567-79, 1977

81. Anger WK, Jordan MK, Lynch DM: Effects of inhalation exposures and intraperitoneal injections of methyl n-amyl ketone on MULT FRFI response rates in rats. Abstract of the paper presented at Midwestern Association of Behavior Analysis, Chicago, May 1977, 2 pp

82. Johnson BL, Setzer JV, Lewis TR, Hornung RW: An Electrodiagnostic Study of the Neurotoxicity of Methyl n-Amyl Ketone. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Biomedical and Behavioral Science, Aug 1977, 20 pp

83. DiVincenzo GD, Kaplan CJ, Dedinas J: Characterization of the metabolites of methyl n-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. Toxicol Appl Pharmacol 36:511-22, 1976

84. Herskowitz A, Ishii N, Schaumberg H: n-Hexane neuropathy--A syndrome occurring as a result of industrial exposure. N Engl J Med 285:82-85, 1971

85. DiVincenzo GD, Hamilton ML, Kaplan CJ, Dedinas J: Metabolic fate and disposition of 14C-labeled methyl n-butyl ketone in the rat. Toxicol Appl Pharmacol 41:547-60, 1977

86. Krasavage WJ, O'Donoghue JL, Terhaar CJ: The Relative Neurotoxicity of Methyl n-Butyl Ketone and Its Metabolites. Abstract of the paper presented at the Seventeenth Annual Meeting of the Society of Toxicology, San Francisco, Mar 12-16, 1978, 3 pp

87. Couri D, Hetland LB, Abdel-Rahman MS, Weiss, H: The influence of inhaled ketone solvent vapors on hepatic microsomal biotransformation activities. Toxicol Appl Pharmacol 41:285-89, 1977

88. Treon JF, Crutchfield WE Jr, Kitzmiller KV: The physiological response of rabbits to cyclohexane, methylcyclohexane, and certain derivatives of these compounds--I. Oral administration and cutaneous application. J Ind Hyg Toxicol 25:199-214, 1943

89. Elliott TH, Parke DV, Williams RT: Studies in detoxication--79. The metabolism of cyclo[14C]hexane and its derivatives. Biochem J 72:193-200, 1959

90. James SP, Waring RH: The metabolism of alicyclic ketones in the rabbit and rat. Xenobiotica 1:573-80, 1971

91. Abdel-Rahman MS, Hetland LB, Couri D: Toxicity and metabolism of methyl n-butyl ketone. Am Ind Hyg Assoc J 37:95-102, 1976

92. Spencer PS, Schaumburg HH: Experimental neuropathy produced by 2,5-hexanedione--A major metabolite of the neurotoxic industrial solvent methyl n-butyl ketone. J Neurol Neurosurg Psychiatry 38:771-75, 1975

93. McCann J, Choi E, Yamasaki E, Ames BN: Detection of carcinogens as mutagens in the Salmonella/microsome test--Assay of 300 chemicals. Proc Nat Acad Sci U S A 72:5135-39, 1975

94. Van Duuren BL, Sivak A, Katz C, Melchionne S: Cigarette smoke carcinogenesis--Importance of tumor promoters. J Natl Cancer Inst 47:235-40, 1971

95. McLaughlin J Jr, Marliac J-P, Verrett MJ, Mutchler MK, Fitzhugh OG: Toxicity of fourteen volatile chemicals as measured by the chick embryo method. Am Ind Hyg Assoc J 25:282-84, 1964

96. DiPaolo JA, Donovan P, Nelson R: Quantitative studies of in vitro transformation by chemical carcinogens. J Natl Cancer Inst 42:867-74, 1969

97. Schwetz BA, Leong BKJ, Gehring PJ: Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28:452-64, 1974

98. Griggs JH, Weller EM, Palmisano PA, Niedermeier W: The effect of noxious vapors on embryonic chick development. Ala J Med Sci 8:342-45, 1971

99. Smith AF, Wood R: A simple field test for the determination of acetone vapour in air. Analyst 95:683-90, 1970

100. Smith AF, Wood R: A field test for the determination of some ketone vapours in air. Analyst 97:363-71, 1972

101. Kacy HW Jr, Cope RW: Determination of small quantities of isophorone in air. Ind Hyg 16:55-59, 1955

102. Andrew P, Wood R: A simple field test for the determination of isophorone vapour in air. Analyst 95:691-97, 1970

103. Acetone, Analytical Abstracts. Akron, Ohio, American Industrial Hygiene Association, 1965, 3 pp

104. Maykoski RT, Jacks C: Review of various air sampling methods for solvent vapors. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1970, 11 pp (NTIS AD 752 525)

105. Van Houten R, Lee G: A method for the collection of air samples for analysis by gas chromatography. Am Ind Hyg Assoc J 30:465-69, 1969

106. Erley DS: Infrared analysis of air contaminants trapped on silica gel. Am Ind Hyg Assoc J 23:388-91, 1962

107. Buchwald H: The determination of acetone in air. Analyst 90:422-28, 1965

108. Buchwald H: Activated silica gel as an adsorbent for atmospheric contaminants. Occup Health Rev 17:14-18, 1965

109. Feldstein M, Balestrieri S, Levaggi DA: The use of silica gel in source testing. Am Ind Hyg Assoc J 28:381-85, 1967

110. Parkes DG, Ganz CR, Polinsky A, Schulze J: A simple gas chromatographic method for the analysis of trace organics in ambient air. Am Ind Hyg Assoc J 37:165-73, 1976

111. Fraust CL, Hermann ER: Charcoal sampling tubes for organic vapor analysis by gas chromatography. Am Ind Hyg Assoc J 27:68-74, 1966

112. Sadenwasser JL: Solvent vapor analysis using activated charcoal tubes. Am Ind Hyg Assoc J 31:533-34, 1970

113. White LD, Taylor DG, Mauer PA, Kupel RE: A convenient optimized method for the analysis of selected solvent vapors in the industrial atmosphere. Am Ind Hyg Assoc J 31:225-32, 1970

114. Part II--Standards completion program validated methods, in NIOSH Manual of Analytical Methods, ed 2, DHEW (NIOSH) publication No. 77-157-B. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Measurements Research Branch, 1977, vol 2, pp S1-1 to S1-8,S3-1 to S3-8,S12-1 to S12-9,S15-1 to S15-9,S18-1 to S18-8,S19-1 to S19-8,S20-1 to S20-8,S55-1 to S55-9

115. Part II--Standards completion program validated methods, in NIOSH Manual of Analytical Methods, ed 2, DHEW (NIOSH) publication No. 77-157-C. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Measurements Research Branch, 1977, vol 3, pp S178-1 to S178-9,S358-1 to S358-8,S367-1 to S367-8

116. Leidel NA, Busch KA, Lynch JR: Occupational Exposure Sampling Strategy Manual, DHEW (NIOSH) publication No. 77-173. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1977, 132 pp

117. Haughton CO: Estimation of acetone. Ind Eng Chem Anal Ed 9:167-68, 1937

118. Goodwin LF: The analysis of acetone by Messinger's method. J Am Chem Soc 42:39-45, 1920

119. Mesityl oxide, Analytical Abstracts. Akron, Ohio, American Industrial Hygiene Association, 1965, 1 p

120. Methyl ethyl ketone (Butanone), Analytical Abstracts. Akron, Ohio, American Industrial Hygiene Association, 1965, 2 pp

121. Haidle CW, Knight SG: A colorimetric assay for 2-heptanone and other ketones. Biochim Biophys Acta 39:536-37, 1960

122. Isophorone, Analytical Abstracts. Akron, Ohio, American Industrial Hygiene Association, 1965, 2 pp

123. 1977 OSHA Concentration Limits for Gases--Incorporating Infrared Analytical Data for Compliance Testing and Other Applications, rev. Norwalk, Conn, Wilks Scientific Corp, 1977, 1 p

124. Chemical indicator tubes for measurement of the concentration of toxic substances in air. Ann Occup Hyg 16:51-62, 1973

125. Documentation of the NIOSH Validation Tests, DHEW (NIOSH) publication No. 77-185. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1977

126. McDonald IA, Hackett LP, Dusci LJ: The identification of acetone and the detection of isopropanol in biological fluids by gas chromatography. Clin Chim Acta 63:235-37, 1975

127. Cooper CV, White LD, Kupel RE: Qualitative detection limits for specific compounds utilizing gas chromatographic fractions, activated charcoal and a mass spectrometer. Am Ind Hyg Assoc J 32:383-86, 1971

128. Rosensteel RE: Magnavox Company of Tennessee--Andrews, North Carolina, Health Hazard Evaluation/Toxicity Determination report No. 73-178-158. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1974, 11 pp

129. Hervin RL, Reifschneider R: Steel Tool and Engineering Company--Taylor, Michigan, Health Hazard Evaluation/Toxicity Determination report No. 72-42-76. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1973, 13 pp

130. Ruhe RL: General Motors Corporation--Vandalia, Ohio, Health Hazard Evaluation/Toxicity Determination report No. 73-83-144. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1974, 7 pp

131. Okawa MT, Shama SK: Sun Products Corporation--Barberton, Ohio, Health Hazard Evaluation/Toxicity Determination report No. 72-12-26. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1973, 17 pp

132. Butler GJ, Taylor JS: Uniroyal Incorporated--Mishawaka, Indiana, Health Hazard Evaluation/Toxicity Determination report No. 72-13-27. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1973, 21 pp

133. Gunter BJ: Raven Industries, Inc--Sioux Falls, South Dakota, Health Hazard Evaluation/Toxicity Determination report No. 73-126-186. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1975, 6 pp

134. Gunter BJ, Philbin EJ, Lowry LK, Tolos WP: Redfield Company--Denver, Colorado, Health Hazard Evaluation/Toxicity Determination report No. 76-99-397. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation and Technical Assistance Branch, 1977, 26 pp

135. Okawa MT: Del Monte Corporation--Oakland, California, Health Hazard Evaluation/Toxicity Determination report No. 74-113-192. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1975, 7 pp

136. Apol AG: Ford Motor Company--Lorain, Ohio, Health Hazard Evaluation report No. 72-40. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1973, 18 pp

137. Rivera RO, Rostand R: Hillerich and Bradsby Company--Jeffersonville, Indiana, Health Hazard Evaluation/Toxicity Determination report No. 74-121-203. Springfield, Va, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1975, 11 pp

138. Rivera RO: GAF Corporation, Equipment Manufacturing Plant--Vestal, New York, Health Hazard Evaluation/Toxicity Determination report No. 74-135-226. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1975, 16 pp

139. Gunter BJ, Lucas JB: Head Ski Company--Boulder, Colorado, Health Hazard Evaluation/Toxicity Determination report No. 73-84-119. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1974, 19 pp

140. Okawa MT, Bodner A: Artcraft Company--Los Angeles, California, Health Hazard Evaluation/Toxicity Determination report No. 73-134-98. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1973, 4 pp

141. Cohen SR, Vandervort R: North American Rockwell, Reinforced Plastic Operation--Ashtabula, Ohio, Health Hazard Evaluation report No. 72-68. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1972, 91 pp

142. Okawa MT: Pacific Moulded Products Company--Los Angeles, California, Health Hazard Evaluation Determination report No. 73-169-122. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1974, 5 pp

143. Marceleno T, Mallov JS: Survey of Moran Paint Division, Carboline Company--Xenia, Ohio. Cincinnati, US Dept of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Field Studies and Clinical Investigations, 1975, 81 pp

144. Hervin RL, Shama SK, Ruhe RL: Aerosol Techniques, Inc--Danville, Illinois, Health Hazard Evaluation report No. 71-25-20. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, 1972, 26 pp

145. Plant observation reports and evaluation. Menlo Park, Calif, SRI International, 1978 (submitted to NIOSH under Contract No. CDC-99-74-31)

146. Anania TL, Tanaka S: Borden Chemical Company--Columbus Coated Fabric Division--Columbus, Ohio, Health Hazard Evaluation Determination report No. 77-8-422. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1977, 13 pp

147. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 14. Lansing, Mich, ACGIH, 1976, pp 1-1 to 14-8

148. American National Standards Institute Inc: Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971. New York, ANSI, 1971, 63 pp

149. National Electrical Code--1978 Edition, NFPA No. 70-1978. Boston, National Fire Protection Association, 1978

150. Ketones, report No. F-41971A. New York, Union Carbide, Chemical Plastics, 1975, 24 pp

151. Properties and Essential Information for Safe Handling and Use of Acetone, Chemical Safety Data Sheet SD-87. Washington, DC, Manufacturing Chemists' Association Inc, 1962, 13 pp

152. Properties and Essential Information for Safe Handling and Use of Methyl Ethyl Ketone, Chemical Safety Data Sheet SD-83. Washington, DC, Manufacturing Chemists' Association Inc, 1961, 15 pp

153. McFee DR: How well do gloves protect hands--Against solvent?--Tests of Argonne National Laboratory reveal some surprising results. J Am Soc Saf Eng 9:11-16, 1964

154. Sansone EB, Tewari YB: The permeability of laboratory gloves to selected solvents. Am Ind Hyg Assoc J 39:169-74, 1978

155. Nelson GO, Harder CA: Respirator cartridge efficiency studies--VI. Effect of concentration. Am Ind Hyg Assoc J 37:205-16, 1976

156. Cook WA: Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14:936-46, 1945

157. American Conference of Governmental Industrial Hygienists: Report of the Sub Committee on Threshold Limits, in Proceedings of the Eighth Annual Meeting of the American Conference of Governmental Industrial Hygienists, Chicago, Apr 7-13, 1946, pp 54-55

158. American Conference of Governmental Industrial Hygienists: Threshold Limit Values Adopted at April 1948 Meeting of American Conference of Governmental Industrial Hygienists, Boston, Massachusetts. Boston, ACGIH, 1948, 3 pp

159. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1953. Arch Ind Hyg Occup Med 8:296-98, 1953

160. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of Threshold Limit Values. Cincinnati, ACGIH 1962, pp 2-3,16,31-32,39,54-55,60,64-65,70,81,90-91

161. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1958. AMA Arch Ind Health 18:178-82, 1958

162. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of Threshold Limit Values, rev. Cincinnati, ACGIH, 1966, pp 2-3,22-23,51-52,55,65-66,100-01, 110,118-19,122,151

163. American Conference of Governmental Industrial Hygienists: Report of TLV Committee--May, 1977. Cincinnati, ACGIH, 1977, 2 pp

164. American Conference of Governmental Industrial Hygienists: TLVs--Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1976. Cincinnati, ACGIH, 1976, pp 9-15,18-23

165. Occupational Exposure Limits for Airborne Toxic Substances, Occupational Safety and Health Series, No. 37. Geneva, International Labour Office, 1977, pp 11-35,56-57,82-85, 98-99,122-23,126-27,132-33,140-41,168-69

166. American Conference of Governmental Industrial Hygienists: Threshold Limit Values of Air-borne Contaminents [sic] for 1968--Recommended and Intended Values. Cincinnati, ACGIH, 1968, pp 5-11,14-17

167. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1961. Cincinnati, ACGIH, 1961, pp 3-5

168. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom air, ed 3, 1971. Cincinnati, ACGIH, 2nd Printing, 1974, pp 66,70,126-27,200,313-14,327

169. Schrenk HH, Yant WP, Patty FA: Acute response of guinea pigs to vapors of some new commercial organic compounds. Public Health Rep 51:624-31, 1936

170. American Conference of Governmental Industrial Hygienists: 1947 M.A.C. Values. Ind Hyg Newsletter 7:15-16, 1947

171. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, ACGIH, 1971, pp 29,66,87,126-27,140,156-57,200

172. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1956. AMA Arch Ind Health 14:186-89, 1956

173. American Conference of Governmental Industrial Hygienists: TLVs--Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1973. Cincinnati, ACGIH, 1973, pp 10-23,26-27,36-39

174. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1960. Presented at the Twenty-second Annual Meeting of the American Conference of Governmental Industrial Hygienists, Rochester, NY, Apr 23-26, 1960, 9 pp

175. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1963. J Occup Med 5:491-98, 1963

176. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1955. AMA Arch Ind Health 11:521-24, 1955

177. Acetone substituted aliphatic alcohols, in Von Oettingen WF: The Aliphatic Alcohols--Their Toxicity and Potential Dangers in Relation to Their Chemical Constitution and Their Fate in Metabolism, NIH bulletin No. 281. Federal Security Agency, US Public Health Service, National Institute of Health, Experimental Biology and Medicine Institute, Laboratory of Physical Biology, 1943, p 139

178. American Conference of Governmental Industrial Hygienists: TLVs--Threshold Limit Values for Substances in Workroom Air Adopted by ACGIH for 1972. Cincinnati, ACGIH, 1972, pp 8-23

179. Duckett S, Williams N, Francis S: Peripheral neuropathy associated with inhalation of methyl-n-butyl ketone. Experientia 30:1283-84, 1974

180. Scheflan L, Jacobs MB: The Handbook of Solvents. Huntington, NY, Robert E Krieger Publishing Co, 1953, pp 12-14,85-87,152-53,234,424-25,433,471-72,491-92,541-42,582-83

181. Ketones, in Gafafer WM (ed.): Occupational Diseases--A Guide to Their Recognition, PHS bulletin No. 1097. US Dept of Health, Education, and Welfare, Public Health Service, 1964, pp 168-70

182. Chemical Data Guide for Bulk Shipment by Water, report No. CG-388. US Dept of Transportation, Coast Guard, 1976, pp 5,72,77

183. [Maximum Work Place Concentration 1976--Senate Commission for the Study of Harmful Work Substances, Communication XII.] Bonn-Bad Godesberg, Federal Republic of Germany, German Research Assoc, 1976, 50 pp

184. Wyart JW, Dante MF: Solvents, industrial, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1967, vol 18, pp 564-88

185. Dean JA (ed.): Lange's Handbook of Chemistry, ed 11. New York McGraw-Hill Book Co, 1973, pp 7-58 to 7-59,7-142 to 7-145,7-268 to 7-273,7-276 to 7-277,7-282 to 7-283

186. Key MM, Henschel AF, Butler J, Ligo RN, Tabershaw IR (eds.): Occupational Diseases--A Guide to Their Recognition, DHEW (NIOSH) publication No. 77-181. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1977, pp 134-37,185,191-93

IX. APPENDIX I

SAMPLING AND ANALYSIS FOR SELECTED KETONES

The following method for 12 selected ketones is adapted from NIOSH methods validated for 11 of the compounds [114,115]. Mention of company name or product does not constitute endorsement by NIOSH.

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the organic vapors present.

(b) The charcoal in the tube is transferred to a small, stoppered glass sample container and desorbed with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

(a) This method was validated for the individual ketones over the range presented in Table IX-1. An atmospheric temperature and pressure of approximately 25 C and 761 mmHg and a sample size of 10-12 liters were used. The method is capable of measuring much lower concentrations, but they have not been validated. Methyl n-butyl ketone, for example, is measurable at a concentration of 4 mg/cu m provided desorbing efficiency is

TABLE IX-1

RANGE, COEFFICIENTS OF VARIATIONS, AND STANDARD DEVIATION OF THE RECOMMENDED SAMPLING AND ANALYTICAL METHOD FOR KETONES

Ketone	Validated Range (mg/cu m)	Probable Range (mg/cu m)	Coefficient of Variation	Standard Deviation*	Deviation From True Values	Reference
Acetone	1,200-4,500	350-5,000	0.082	4.1%**	-2%	114
Methyl ethyl ketone	380-1,240	70-1,500	0.072	46 mg/cu m	+9%	114
Methyl n-propyl ketone	395-1,570	70-2,100	0.063	21 mg/cu m	-1.3%	114
Methyl n-butyl ketone	188-790	40-1,200	0.053	22 mg/cu m	-0.5%	115
Methyl n-amyl ketone	200-925	50-1,000	0.0660	15.7 mg/cu m	+2%	114
Methyl isobutyl ketone	208-836	40-1,230	0.064	17 mg/cu m	-4.8%	114
Methyl isoamyl ketone	NO DATA AVAILABLE					
Diisobutyl ketone	145-582	30-1,000	0.070	20.3 mg/cu m	-1.4%	115
Cyclohexanone	98-392	10-500	0.062	7.4 mg/cu m	-6.3%	114
Mesityl oxide	45-210	10-300	0.0708	7.8 mg/cu m	+7%	114
Diacetone alcohol	140-510	24-750	0.104	24.1 mg/cu m	-11.9%	114
Isophorone	68-283	2-400	0.058	8 mg/cu m	+5%	115

*At current Federal standard
**Relative standard deviation

adequate since the lower limit of detection for the NIOSH validated method has been stated as 0.01 mg/cu m [146]. Desorption efficiency must be determined over the actual range of the samples.

(b) The useful range of the sampling method depends largely on the adsorptive capacity of the charcoal tube. The total amount of ketone collected will vary with the sampling rate and with the concentrations of ketones and other substances, particularly water vapor, in the air. Experimental results on breakthrough are listed in Table IX-2 and were determined with a relative humidity of less than 15% and at normal conditions. If a particular atmosphere is suspected of containing a large amount of ketone, a smaller sample volume should be collected.

Interference

(a) When the amount of water in the air is so great that condensation actually occurs in the charcoal tube, ketone vapors will not be trapped efficiently.

(b) When two or more compounds are known or suspected to be present in the air, such information, including their suspected identities, should be transmitted with the sample.

(c) It must be emphasized that any compound that has the same retention time as the ketone at the operating conditions described in this method will interfere. Hence, retention time data on a single column, or even on a number of columns, cannot always be considered proof of chemical identity.

(d) If interference is known to occur with the analysis in question, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

Precision and Accuracy

The coefficients of variation, standard deviations, and deviations from "true" values for the combined sampling and analytical method are listed in Table IX-1. The standard deviation at the present Federal standard is also reported. The data in Table IX-1 for mesityl oxide, methyl n-butyl ketone, methyl n-amyl ketone, and diacetone alcohol are based on experiments using an internal standard.

Advantages and Disadvantages of the Method

(a) The sampling device is small and portable and involves no liquids. Analytical interferences are usually minimal, and most of those that do occur can be eliminated by altering the chromatographic conditions. The tubes are analyzed by means of a quick, instrumental method. In some cases, by adjusting chromatographic conditions, the method can also be used for the simultaneous analysis of two or more substances suspected to be present in the same sample, provided that each substance can be efficiently desorbed with the same desorbing medium.

TABLE IX-2

BREAKTHROUGH DATA IN CHARCOAL TUBE SAMPLING OF THE KETONES

Ketone	Amount of Ketone in 1st Section (mg)	Influent Test Atmosphere (mg/cu m)	Sampling Rate (liters/min)	Breakthrough Time* (min)	Reference
Acetone	18	4,300	0.195	22	114
Methyl ethyl ketone	19	1,260	0.17	86	114
Methyl n-propyl ketone	27	1,450	0.19	100	114
Methyl n-butyl ketone	35	790	0.187	240**	115
Methyl n-amyl ketone	15	925	0.2	>180**	114
Methyl isobutyl ketone	20	1,145	0.19	91.7	114
Diisobutyl ketone	25	582	0.20	219	115
Cyclohexanone	26***	-	-	-	114
Mesityl oxide	9.6	210	0.2	240	114
Diacetone alcohol	24	507	0.2	>240**	114
Isophorone	13	283	0.19	>240**	115

*When concentration of ketone in effluent reaches 5% of that in influent
**No breakthrough in stated time
***In 1st section when breakthrough occurred

(b) One disadvantage of the method is that the amount of sample that can be taken is limited by the mass of ketone that the tube will hold before overloading. This sample size is dependent on the types and concentrations of the contaminants in the workplace air. When the sample value obtained for the backup section of the charcoal trap exceeds 25% of that found on the front section, sample loss must be suspected.

(c) The precision of the method is limited by the reproducibility of the pressure drop across the tubes. If the pump is calibrated for one tube only, variations in pressure drop from tube to tube will result in different flowrates and cause volumes to be imprecise.

Apparatus

(a) An approved and calibrated personal sampling pump with a flow that can be determined to within 5% at the recommended flowrate.

(b) Charcoal tubes: glass tube with both ends flame-sealed, 7 cm long with a 6-mm outer diameter and a 4-mm inner diameter, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The absorbing front section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in the front of the tube. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/ minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Chromatographic column:

(1) 20-feet x 1/8-inch stainless steel, packed with 10% FFAP on 80/100 mesh Chromosorb W AW-DMCS (acid-washed dimethylchlorosilated) for methyl n-butyl ketone.

(2) 4-feet x 1/4-inch stainless steel, packed with 50/80 mesh Porapak, Type Q, for acetone.

(3) 10-feet x 1/8-inch stainless steel, packed with 10% FFAP on 80/100 mesh Chromosorb W DMCS, for the other 10 ketones.

(e) An electronic integrator or some other suitable method for measuring peak areas.

(f) One-milliliter glass sample containers with glass stoppers or Teflon-lined caps.

(g) Microliter syringes: 10-μl and other convenient sizes for making standards.

(h) Pipets: 0.5-ml delivery pipets or 1.0-ml type graduated in 0.1-ml increments.

(i) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

Reagents

(a) Chromatographic quality carbon disulfide (containing 5% 2-propanol for diacetone alcohol analysis).

(b) Ketone, reagent grade.

(c) Purified nitrogen.

(d) Prepurified hydrogen.

(e) Filtered compressed air.

(f) n-Tridecane (99+%) for use as internal standard.

(g) n-Heptane, reagent grade.

Procedure

(a) Cleaning of Equipment. Detergent wash all glassware used for the laboratory analysis and rinse thoroughly with tapwater and distilled water.

(b) Calibration of Personal Pumps. Calibrate each personal pump with a representative charcoal tube in line as shown in Figure XI-1. This will minimize errors associated with uncertainties in the sample volume collected.

(c) Collection and Shipping of Samples

(1) Immediately before sampling, break the ends of the tube to provide an opening at least one-half the internal diameter of the tube (2 mm).

(2) Use the smaller section of charcoal as a backup and position it nearest the sampling pump.

(3) Place the charcoal tube in a vertical direction during sampling to minimize channeling through the charcoal.

(4) Do not pass air being sampled through any hose or tubing before entering the charcoal tube.

(5) A maximum sample size of 10-12 liters is recommended. This size can be attained by sampling at a rate of 0.20 liter/minute. The flowrate should be known with an accuracy of at least 5%.

(6) Record the temperature and pressure of the atmosphere being sampled.

(7) Cap the charcoal tubes with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(8) Handle at least one tube in the same manner as the sample tube (break, seal, and transport), but do not draw air through this tube. Label this tube as a blank.

(9) Pack capped tubes tightly before they are shipped to minimize tube breakage during shipping.

(10) Submit a sample of the bulk material to the laboratory in a glass container with a Teflon-lined cap. Do not transport this sample in the same container as the charcoal tubes.

(d) Analysis of Samples

(1) Preparation of Samples. Sample tubes will be received opened but protected by plastic caps. Remove the plastic cap from the front section, discard the glass wool in front of the charcoal, and transfer the charcoal in the first (larger) section to a 1-ml stoppered sample container. Remove and discard the separating section of foam; transfer the second section to another stoppered container. Analyze these two sections separately.

(2) Desorption of Samples. Prior to analysis, pipet 0.5 ml of carbon disulfide (1.0 ml for mesityl oxide, methyl n-butyl ketone, diacetone alcohol, and methyl n-amyl ketone analysis) into each sample container. For the internal standard method, use a 0.1% solution of the internal standard in the eluent. Tests have indicated that desorption is

complete in 30 minutes if the sample is stirred occasionally during this period. If an automatic sample injector is used, cap the sample vials as soon as the solvent is added to minimize volatilization.

EXTREME CAUTION MUST BE EXERCIZED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(3) Chromatograph Conditions. The typical operating conditions for the gas chromatograph for each ketone are listed in Table IX-3.

(4) Injection. The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blow back or distillation within the syringe needle, one should employ the solvent flush injection technique, possibly using a syringe guide for ease of performance. First flush the 10-μl syringe with solvent several times to wet the barrel and plunger. Draw 3 μl of solvent into the syringe to increase the accuracy and reproducibility of the injected sample volume. Remove the needle from the solvent, and pull the plunger back about 0.2 μl to separate the solvent flush from the sample with a pocket of air to be used as a marker. Immerse the needle in the sample, and withdraw a 5-μl aliquot, taking into consideration the volume of the needle, since the sample in the needle will be completely

TABLE IX-3

TYPICAL CHROMATOGRAPH CONDITIONS FOR KETONES

Ketone	Gas Flow (ml/min)			Temperature (C)			Reference
	Carrier Nitrogen	Hydrogen*	Air*	Injector	Detector	Column	
Acetone	50 at 60 psig	65 at 24 psig	500 at 50 psig	175	200	125	114
Methyl ethyl ketone	"	"	"	100	200	50	114
Methyl n-propyl ketone	"	"	"	190	250	60	114
Methyl n-butyl ketone	30 at 60 psig	35 at 25 psig	400 at 60 psig	225	250	80	115
Methyl n-amyl ketone	30 at 80 psig	30 at 50 psig	300 at 50 psig	200	300	120	114
Methyl isobutyl ketone	50 at 60 psig	65 at 24 psig	500 at 50 psig	260	193	65	114
Methyl isoamyl ketone	"	"	"	200	300	120	114
Diisobutyl ketone	50 at 60 psig	65 at 24 psig	500 at 50 psig	230	241	71	115
Cyclohexanone	"	"	"	220	255	110	114
Mesityl oxide	30 at 80 psig	30 at 50 psig	300 at 50 psig	200	300	120	114
Diacetone alcohol	"	"	"	200	300	120	114
Isophorone	50 at 60 psig	65 at 24 psig	500 at 50 psig	255	250	167	115

*Flow to detector

injected. After removing the needle from the sample and prior to injection, pull the plunger back 1.2 μl to minimize evaporation of the sample from the tip of the needle. Observe that the sample occupies 4.9-5.0 μl in the barrel of the syringe. Make duplicate injections of each sample and standard. No more than a 3% difference in area is to be expected.

An automatic sample injector can be used if it is shown to give reproducibility at least as good as the solvent flush technique. In this case, 2-μl injections are satisfactory.

(5) Measurement of Area. Measure the area of the sample peak with an electronic integrator or some other suitable form of area measurement and read preliminary results from a standard curve prepared as discussed below.

(e) Determination of Desorption Efficiency

(1) Importance of Determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process for a given compound, provided the same batch of charcoal is used.

(2) Effect of Time. The amount of cyclohexanone found on the charcoal tubes decreased with time. The storage stability of the other ketones was not tested. Therefore, in determining desorption efficiency for field samples, the spiked tubes should be stored under the same conditions as the field samples (for example, time and temperature of storage should be the same).

(3) Procedure for Determining Desorption Efficiency. Measure an amount of activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) into a 7-cm, 4-mm inner diameter glass tube, flame-sealed at one end. This charcoal must be from the batch used in obtaining the samples, and it can be obtained from unused charcoal tubes. Cap the open end with Parafilm. Inject a known amount of the ketone directly into the activated charcoal with a microliter syringe, and cap the tube with more Parafilm. For mesityl oxide analysis, inject an 8% stock solution of mesityl oxide in n-heptane in the desired amount. For diacetone alcohol, use a 600 mg/ml stock solution of the analyte in n-heptane. In experiments conducted to validate the method, the amount injected was approximately equivalent to that present in a 10- or 12-liter sample at the selected level.

Prepare six tubes, each containing an amount of ketone that would be expected in a 10- to 12-liter sample of air at 0.5X, 1.0X, and 2.0X the recommended workplace environmental limit specified for the ketone of interest in Chapter I. Allow these tubes to stand at least overnight to assure complete sorption of the analyte onto the charcoal. These tubes are referred to as the samples. Treat a parallel blank tube in the same manner but add no ketone to it. Desorb and analyze the sample and blank tubes in exactly the same manner as the sampling tube.

Prepare two or three standards by injecting the same volume of compound into 0.5 ml (or 1.0 ml) of carbon disulfide. Analyze these standards with the samples.

The desorption efficiency equals the average weight in milligrams recovered from the tube divided by the weight in milligrams added to the tube, or

$$\text{Desorption Efficiency} = \frac{\text{average weight (mg) recovered}}{\text{weight (mg) added}}$$

The desorption efficiency is dependent on the amount of analyte collected on the charcoal. Plot the desorption efficiency versus weight of analyte found. Use this curve to correct for adsorption losses.

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/0.5 ml (or mg/1.0 ml as appropriate) of carbon disulfide, because samples are desorbed in this amount of carbon disulfide. The density of the ketone is used to convert mg into μl for easy measurement with a microliter syringe. When using an internal standard, prepare a final concentration of 0.1% standard in the desorbent. Prepare a series of standards, varying in concentration over the range of interest, and analyze them under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/0.5 ml versus peak area; a linear response is expected with the ketones.

> Note: If an internal standard is not used in the method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-ionization detector response. In the case of the internal standard method, plot concentration versus the ratio of peak area of ketone to peak area of the internal standard.

Calculations

(a) Read the weight, in mg, corresponding to each peak area from the standard curve. No volume corrections are needed, because the standard curve is based on mg/0.5 ml (or mg/1.0 ml) of carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

(b) Corrections for the blank must be made for each sample:

$$\text{mg} = \text{mg sample} - \text{mg blank}$$

where:

mg sample = mg found in front section of sample tube

mg blank = mg found in front section of blank tube

Use a similar procedure for the backup sections.

(c) Add the weights found in the front and backup sections to get the total weight in the sample.

(d) Read the desorption efficiency from the curve for the amount found in the front section. Divide the total weight by this desorption efficiency to obtain the total mg/sample:

$$\text{corrected mg/sample} = \frac{\text{total weight}}{\text{desorption efficiency}}$$

(e) The concentration of the ketone in the sampled air can be expressed in mg/cu m:

$$\text{mg/cu m} = \frac{\text{total mg} \times 1{,}000 \text{ (liters/cu m)}}{\text{air volume sampled (liters)}}$$

(f) Another method of expressing concentration is ppm:

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{FW} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure (mmHg) of air sampled

T = temperature (C) of air sampled

24.45 = molar volume (liters/mole) at 25 C and 760 mmHg

FW = formula weight

760 = standard pressure (mmHg)

298 = standard temperature (K)

X. APPENDIX II

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity,

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or Mine Safety and Health Administration approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA		
BOILING POINT 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O % BY WT
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE 1)
APPEARANCE AND ODOR		

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

XI. TABLES AND FIGURE

TABLE XI-1

SYNONYMS AND STRUCTURAL FORMULAS FOR THE KETONES

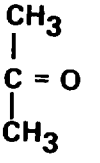
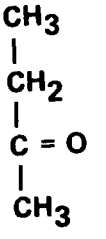
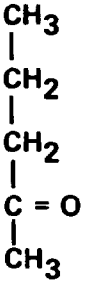
Ketone Name and Formula	Synonyms	Structural Formula
Acetone C_3H_6O	2-Propanone Aceton (German, Dutch, Polish) Dimethylketal Dimethyl ketone Beta-ketopropane Methyl ketone Pyroacetic ether Pyroacetic spirit	
Methyl ethyl ketone C_4H_8O	2-Butanone or Butanone Methyl acetone Aethylmethylketon (German) Butanone Ethyl methyl cetone (French) Ethylmethylketon (Dutch) Ethyl methyl ketone MEETCO MEK Metiletilchetone (Italian) Metyloetylketon (Polish)	
Methyl propyl ketone $C_5H_{10}O$	2-Pentanone Pentanone 2-Pentanon (German) Ethyl acetone Methyl propanone Methyl-propyl-cetone (French) Metylopropylketon (Polish) Methylpropyl ketone 2-Methyl cyclohexanone 2-Methyl-cyclohexanon (German, Dutch) 2-Metilcicloesanone (Italian)	

TABLE XI-1 (CONTINUED)

SYNONYMS AND STRUCTURAL FORMULAS FOR THE KETONES

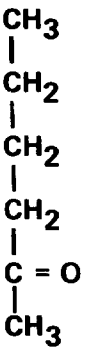
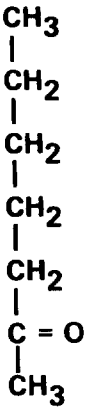
Ketone Name and Formula	Synonyms	Structural Formula
Methyl n-butyl ketone $C_6H_{12}O$	2-Hexanone n-Butyl methyl ketone MBK Methyl butyl ketone MNBK Methyl 2-butyl ketone Methyl butanone	
Methyl amyl ketone $C_7H_{14}O$	2-Heptanone Amyl-methyl-cetone (French) n-Amyl methyl ketone	

TABLE XI-1 (CONTINUED)

SYNONYMS AND STRUCTURAL FORMULAS FOR THE KETONES

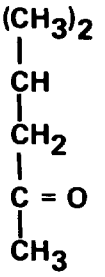
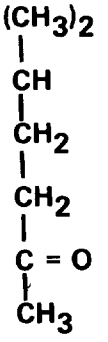
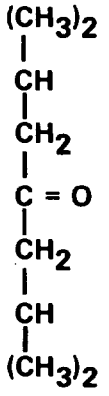
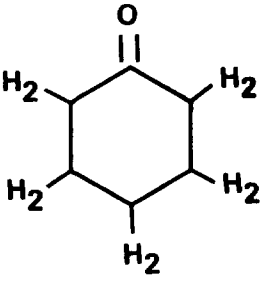
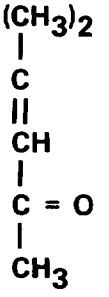
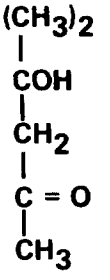
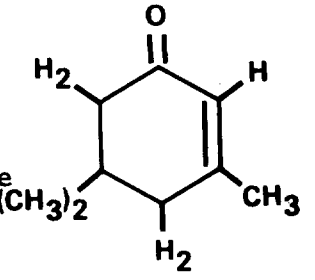
Ketone Name and Formula	Synonyms	Structural Formula
Methyl isobutyl ketone $C_6H_{12}O$	4-Methyl pentanone 4-Methylpentan-2-one Hexon (Czech) Hexone Isobutyl methyl ketone Methyl-isobutyl-cetone (French) Methylisobutylketon (Dutch, German) Metyloizobutyloketon (Polish) 2-Methyl-4-pentanone Metilisobutilchetone (Italian) MIK MIBK	
Methyl isoamyl ketone $CH_3COC_5H_{11}$	5-Methyl-2-hexanone Isoamyl methyl ketone Isopentyl methyl ketone 2-Methyl-5-hexanone MIAK	
Diisobutyl ketone $C_9H_{18}O$	2,6-Dimethyl-4-heptanone Di-isobutyl ketone Isobutyl ketone Isovalerone Valerone Diisobutilchetone (Italian) Di-isobutylcetone (French) Diisobutylketon (Dutch, German) Diisopropylacetone 2,6-Dimethyl-heptan-4-on	

TABLE XI-1 (CONTINUED)

SYNONYMS AND STRUCTURAL FORMULAS FOR THE KETONES

Ketone Name and Formula	Synonyms	Structural Formula
Cyclohexanone $C_6H_{10}O$	Cicloesanone (Italian) Cyclohexanon (Dutch) Cykloheksanon (Polish) Hexanon Nytro-O Ketohexamethylene Nadone Pimelic ketone Pimelin ketone	
Mesityl oxide $C_6H_{10}O$	4-Methyl-3-penten-2-one Isopropylidene acetone Isobutenyl methyl ketone Mesityloxid (German) Mesityloxyde (Dutch) Ossido di mesitile (Italian) Oxyde de mesityle (French)	
Diacetone alcohol $C_6H_{12}O_2$	4-Hydroxy-4-methyl-2-petenone Diacetonalcohol (Dutch) Diacetonalcool (Italian) Diacetonalkohol (German) Diketone alcohol 4-Hydroxy-2-keto-4-methylpentane Tyranton	
Isophorone $C_9H_{14}O$	3,5,5-Trimethyl-2-cyclohexen-1-one Isoacetophorone Isoforon Isoforone (Italian) Isophoron Izoforon 1,1,3-Trimethyl-3-cyclohesene-5-one 3,5,5-Trimethyl-2-cyclohexen-1-on (German)	

Adapted from references 9,11,100,157,158,162,165,180-183

TABLE XI-2

CHEMICAL AND PHYSICAL PROPERTIES OF KETONES

Compound	Formula Weight	Boiling Point (C)	Melting Point (C)	Specific Gravity (20/20 C)	Refractive Index (20 C)	Vapor Pressure (mmHg at 25 C)	Air Saturation (%)	Evaporation Rate (ether=1)	Flashpoint*	Flammable Limits (% v/v)	Water Solubility	Conversion Factors (mg/cu m =1 ppm)
Acetone	58.08	56.1	-95.6	0.7911	1.3589	226.3	29.8	1.9	0	2.15-13	Yes	2.37
Methyl ethyl ketone	72.11	79.6	-86.6	0.8072 (25/25 C)	1.3814 (15 C)	100	13.2	2.7	22 (20)	1.8 -12.0	25.57	2.95
Methyl n-propyl ketone	86.11	102.2	-83.5	0.8064 (20/4 C)	1.3895	16.0	2.1	1.62**	45 (58)	1.55-8.15	5.51	3.52
Methyl n-butyl ketone	100.16	127.5	-56.9	0.8072 (25/4 C)	1.3969 (17.4 C)	3.8	0.5	8.1	73	1.22- 8.0	1.64	4.10
Methyl n-amyl ketone	114.18	150.6	-26.9	0.8166	1.4073	1.6	0.21	17.4	120 (117)	-	0.43	4.67
Methyl iso-butyl ketone	100.16	115.8	-83.5	0.8020	1.3959	7.5	1.0	5.6	64 (74)	1.35- 7.6	1.91 g/100 g	4.10
Methyl iso-amyl ketone	114.18	144	-	0.8132	1.4062	1.52 (20 C)	-	0.4***	(110)	-	Slight	4.67
Diisobutyl ketone	142.24	168.1	-5.9	0.8089	1.421 (15 C)	2.4	0.32	30.8	30.8 (120)	-	Very slight	5.82
Cyclohexanone	98.14	155.6	-45	0.9478 (20/4 C)	1.4500	4.5	0.60	40.6	143 (116)	1.1 (lower)	Slight	4.01
Mesityl oxide	98.14	129.55	-46.4	0.8569	1.444	9.5	1.25	8.4	90 (84)	1.3 - 8.8	Very Slight	4.01
Diacetone alcohol	116.16	169.2	-42.8	0.9406	1.4242	1.2	0.16	60	- (142)	1.8 - 6.9	Yes	4.75
Isophorone	138.21	215.2	-8.1	0.9229	1.4789 (21.5 C)	0.44	0.06	200	184 (205)	0.8 - 3.8	Very Slight	5.65

*Flashpoint, Tag closed cup value (F) with open cup value (F) in parentheses.
**All of the ketones are soluble in inorganic solvents.
***Butyl acetate=1

TABLE XI-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO KETONES

Acetic acid makers	Leather workers, artificial
Acetic anhydride makers	Lubricating oil dewaxer
Acetone workers	Mesityl oxide makers
Acetylene cylinder fillers	Metal cleaners
Adhesive makers	Methyl isobutyl ketone makers
Adipic acid makers	Methyl methacrylate workers
Benzene workers	Nylon makers
Bronzers	Oil processors
Butanone workers	Organic chemical synthesizers
Celluloid makers	Painters
Cellulose acetate makers	Paintmakers
Cellulose cementmakers	Paint remover workers
Chloroform makers	Paraffin processors
Cleaning compound makers	Perfume makers
Colorless synthetic resin makers	Pentanone workers
Cosmetic makers	Pesticide makers
Dewaxers	Petroleum refinery workers
Diacetone alcohol makers	Photographic film makers
Dope workers	Printers
Drug makers	Raincoat makers
Dyemakers	Resin makers
Electronic equipment cleaners	Rubber cement workers
Electronic equipment dryers	Rubber workers
Explosive makers	Shoemakers
Fungicide makers	Solvent workers
Garage mechanics	Smokeless powder makers
Glycol makers	Stain makers
Iodoform makers	Textile makers
Ketone manufacturers	Varnish makers
Lacquerers	Varnish remover workers
Lacquer makers	Vinyl raincoat makers
Lacquer remover workers	Wax makers

Adapted from references 181,186

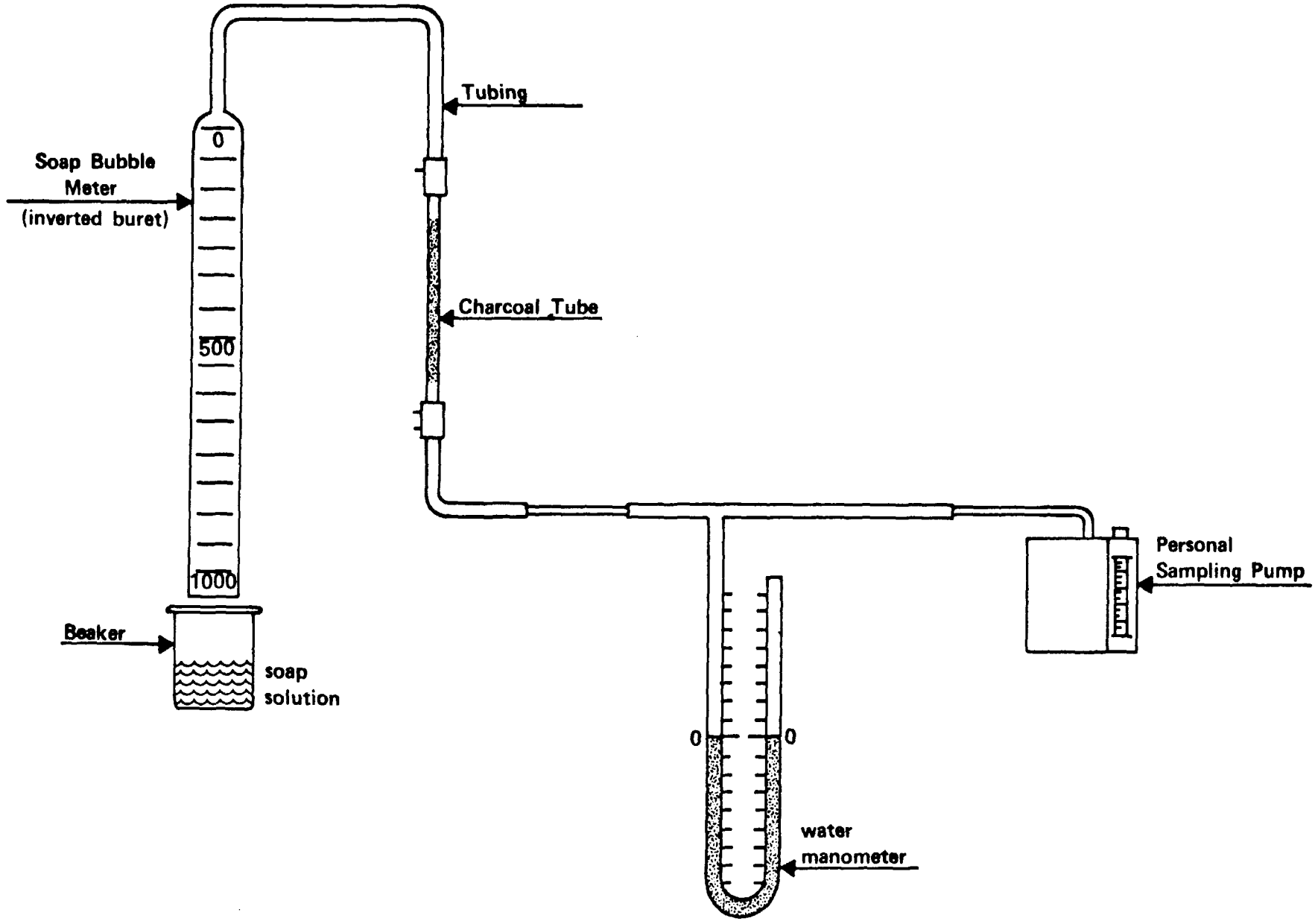


FIGURE XI-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE

☆ U.S. GOVERNMENT PRINTING OFFICE: 1978—757-141/1823

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ROBERT A. TAFT LABORATORIES
4676 COLUMBIA PARKWAY, CINCINNATI, OHIO 45226

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W
HEW 396

DHEW (NIOSH) Publication No. 78-173